Eötvös Loránd University
Faculty of Education and Psychology

Doctoral (Ph.D.) Thesis

KAPITÁNY-FÖVÉNY MÁTÉ

Characteristics of the use of novel psychoactive substances (NPSs) in Hungary

2015

Author:	**Kapitány-Fövény Máté**
Title:	**Characteristics of the use of novel psychoactive substances in Hungary**
Supervisor:	**Prof. Dr. Demetrovics Zsolt**, DSc, professor, Eötvös Loránd University
Doctoral School:	Eötvös Loránd University, Faculty of Education and Psychology, Doctoral School of Psychology
Doctoral Program:	Personality- and Health Psychology Program
Head of Doctoral School and Program:	**Prof. Dr. Oláh Attila**, CSc, professor, Eötvös Loránd University

Members of Reading Committee:

Chair:	**Prof. Dr. Molnár Márk**, DSc, professor, Eötvös Loránd University, MTA Institute of Cognitive Neuroscience and Psychology
Internal reviewer:	**Dr. Felvinczi Katalin**, PhD, associate professor, Eötvös Loránd University
External reviewer:	**Prof. Dr. Rihmer Zoltán**, DSc, professor, Semmelweis University
Secretary:	**Dr. Lisznyai Sándor**, PhD, assistant professor, Eötvös Loránd University
Members:	**Dr. Elekes Zsuzsanna**, DSc, professor, Corvinus University of Budapest **Dr. Hoyer Mária**, PhD, associate professor, Semmelweis University **Dr. Schmelowszky Ágoston,** PhD, associate professor, Eötvös Loránd University

Date of submission: June 2015.

MAGYAR NYELVŰ ÖSSZEFOGLALÁS

Az elmúlt években a drogpiac radikális átalakulását kísérhettük figyelemmel. Újabb és újabb pszichoaktív szerek jelentek meg a rekreációs szcénában, a használatukkal kapcsolatos klinikai tapasztalatok és kutatási eredmények pedig egyre világosabbá tették, hogy számos esetben alakulhatnak ki szomatikus szövődmények és pszichés probémák – többek között függőség és súlyos pszichotikus állapot -, illetve túladagolás esetén halál is bekövetkezhet. Ezen új pszichoaktív szerek (ÚPSZ) népszerűsége javarészt praktikus vagy éppen gazdasági szempontok szerint értelmezhető, mint a legális kockázatok átmeneti hiánya, az alacsony ár, a könnyű hozzáférhetőség vagy az a tény, hogy sok ÚPSZ nem mutatható ki a gyorsteszteken. A könnyű hozzáférhetőségre jó példa, hogy a használók e szereket sokszor interneten keresztül szerezték/szerzik be. Ez a fajta web-alapú marketing, valamint az ÚPSZok iránti internetes érdeklődés azonban nem csak rizikótényezőként fogható fel, hanem egy lehetséges epidemiológiai indikátorként is, amint erre a disszertációmban részletesebben is kitérek.

Az ÚPSZek feltételezett tisztasága és farmakokinetikai jellemzőik szintén vonzóvá tették ezen szereket a használók számára, lévén, hogy az ÚPSZek jelentős része – így például a katinon-származékok is – könnyen átlépnek a vér-agy gáton. Az ÚPSZek népszerűségének elsődleges és legfontosabb magyarázata azonban az, hogy a drogpiacon az elmúlt években megfigyelt heroin, kokain és ecstasy hiány arra ösztönözte a használókat, hogy új szintetikus drogokat próbáljanak ki választott drogjuk helyett. Szerváltásnak hívjuk ezt a jelenséget, és a szakirodalomban elsősorban az intravénás droghasználók szerváltásával találkozhatunk.

A disszertációmban bemutatott kutatások két fő célkitűzést követnek. Elsődleges célként arra keresem a választ, hogy az általam kutatott ÚPSZek, a mefedron és egyéb katinon-származékok, valamint a GHB esetében milyen lehetséges funkciók állhatnak a használat hátterében. Ennek kapcsán feltárom az első és a jelenlegi ÚPSZ használat körülményeit, beleértve a használat társas kontextusát, a szerek jellemző szubjektív és szomatikus hatásait, valamint a használatukhoz köthető pszichiátriai tüneteket. A mefedron esetében megvizsgálom, hogy miként tudja ez a szer helyettesíteni nem csak az ecstasyt és egyéb pszichostimulánsokat, de akár az opiátokat is. A GHB lehetséges funkcionalitásának vizsgálatakor pedig elsősorban a szer szexuális viselkedésre és szubjektív élményekre gyakorolt hatásait tárom fel. A kutatásaim másik célja, hogy három olyan pszichológiai etiológiai modell alkalmazhatóságát teszteljem ÚPSZ használóinak mintáján, melyek mind az addiktológiai kutatás, mind a klinikai gyakorlat szempontjából kiemelt relevanciával bírnak: a) az öngyógyítási (öngyógyszerezési) hipotézis, b) a társas kontextus hatása, c) a traumatikus életesemények szerepe.

Amikor tehát azt feltételezem, hogy a súlyosabb pszichiátriai tünetekkel jellemezhető használók gyakoribb és intenzívebb (pl. intravénás) ÚPSZ használatot mutatnak (lásd: 7.3.-as fejezet), elsősorban a Khantzian-féle öngyógyítási hipotézisre támaszkodom. Amikor az ÚPSZ használat társas kontextusát elemzem, kiemelem a különböző pszichoszociális tényezők jelentőségét mind az ÚPSZ használat kezdete, mind a folytatódó használat szempontjából (lásd: 7.3.-as és 7.6.-os fejezetek). Végül az opiát függő betegek mintáján vizsgált traumatikus életesemények kapcsán azt feltételezem, hogy az ÚPSZ használó betegek intenzívebb érzelmi reakciókkal válaszolnak a megterhelő életeseményekre (lásd: 7.4.-es fejezet).

Disszertációm hat empirikus kutatásból épül fel:

1. Kutatás: Az első kutatás (7.1.-es fejezet) során elsőként a mefedronnal kapcsolatos internetes érdeklődés alakulását vizsgáltam a szer legális és illegális státuszának fényében. A kutatás kapcsán továbbá a GHB-val kapcsolatos internetes keresések és a GHB-intoxikációs esetek közötti együttjárást elemeztem a Google Trends alkalmazás segítségével.

2. Kutatás: A második kutatás (7.2.-es fejezet) a mefedron jellemző szubjektív és szomatikus hatásait tárta fel annak megállapítására, hogy képes-e hatékonyan helyettesíteni a mefedron az olyan entaktogén stimulánsokat, mint az ecstasy. A második és harmadik kutatást 145 rekreációs mefedronhasználó mintáján végeztem, akiket hólabda mintavétellel értünk el.

3. Kutatás: Mivel a második kutatás során magas arányban találtunk intravénás mefedronhasználókat (Kapitány-Fövény és mtsai., 2013a), a harmadik kutatás esetében (7.3.-as fejezet) az intravénás és nem intravénás mefedronhasználók összehasonlítását tűztem ki célul, különös tekintettel a pszichiátriai tünetek súlyosságára. Az első és a jelenlegi mefedronhasználat kapcsán feltártuk továbbá a társas környezet szerepét, valamint – a negyedik kutatással párhuzamban - megvizsgáltuk, hogy képes-e a mefedron a gyakran intravénásan használt szerek – például az opiátok – helyettesítésére.

4. Kutatás: A harmadik kutatásban az intravénás mefedronhasználók között jelentősnek bizonyult az opiáthasználat megjelenése (Kapitány-Fövény és mtsai., megjelenés alatt-a), így kérdésessé vált, hogy a megemelkedett pszichiátriai tünetprofil vajon az intravénás mefedronhasználatnak vagy inkább az opiáthasználatnak tudható-e be inkább. E kérdés eldöntésére a negyedik kutatásban (7.4.-es fejezet) 198 opiátfüggő beteg mintáján vizsgáltuk meg az ÚPSZ – és így a katinon-származékok – használatának pszichiátriai tünetekkel mutatott kapcsolatát. A kutatás során ellenőriztem továbbá mind az öngyógyítási hipotézis alkalmazhatóságát, mind a traumatikus életesemények szerepét az ÚPSZ használat megjelenésében.

5. Kutatás: Az ötödik kutatás (7.5.-ös fejezet) a GHB toxicitásán túl a szer szexuális visszaélések és vagyon elleni bűncselekmények kapcsán játszott szerepét vizsgálta 352 GHB-intoxikált beteg (összesen 408 intoxikációs eset) mintáján. A kutatás során a szándékos és a nem szándékos GHB használati esetek is összehasonlításra kerültek, valamint ellenőriztem a GHB randi-drogként betöltött lehetséges funkcionalitását.

6. Kutatás: Mivel az ötödik kutatás során a GHB randi-drogként betöltött szerepe nem tűnt olyan jelentősnek, mint azt az ezzel kapcsolatos média-beszámolók sugallták, az utolsó, hatodik kutatás során (7.6.-os fejezet) azt vizsgáltuk meg, hogy a szándékos GHB használat milyen hatást gyakorol a használók szexuális viselkedésére és szubjektív élményeire (Kapitány-Fövény és mtsai., megjelenés alatt-b). Ezen kutatás kapcsán tehát 60 rekreációs GHB használó mintáján arra a kérdésre kerestük a választ, hogy a GHB képes-e egyfajta szexuális vágyfokozó szerként funkcionálni. Akárcsak a harmadik kutatás esetében, az első és a jelenlegi használat esetében is megvizsgáltuk a használat társas kontextusát.

A disszertációm konklúziójaként végül egy komplex model keretein belül értelmezem az etiológiai modellek és a használat funkcionalitásának szerepét az ÚPSZ használat alakulásában.

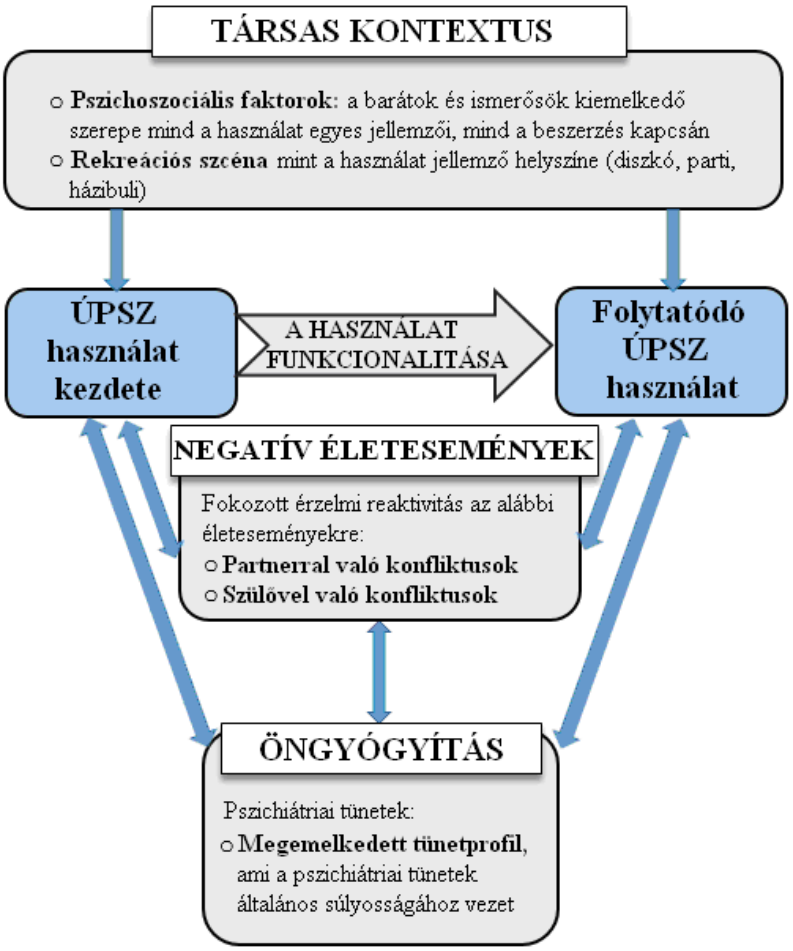


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor, *Prof. Dr. Demetrovics Zsolt*, for his professional and careful guidance, which enabled the making of this thesis. Zsolt – as a supervisor, mentor and friend – smoothed the way for me in the past seven-eight years, while showing the bloom of scientific thinking and prudence. He taught me how to write scientific papers, how to manage data collection, entry and procedure, how to organize international studies and research collaborations.

I also want to thank *Dr. Urbán Róbert* for his great support in statistical analysis and research methodology. I have learnt a lot from him about multivariate statistics and structural equation modeling. Róbert's outstanding expertise in statistics inspired many of us.

Dr. Zacher Gábor helped a lot in finding patients with a history of NPS use and also provided some useful advice regarding the toxicity of the studied NPSs. I want to thank him for that.

I want to thank *Kertész Máté, Marjai Kamilla, Ágoston Csilla, Ispán Viktória, Nemecz Zsuzsanna, Otoltics Zsófia, Diósi Rita, Várkonyi Lilla, Pelbát Gergely, Szabó Anna, Jávorszky Eszter, Menczigár Erika, Ribánszky Róbert, Pataki Patrícia, Kiss Anna, Horváth Janka, Urbán Ágnes, Szentiványi Dóra, Horváth Dorothee, Szilvás Fanni, Tusják Terézia, Mezey Réka, Balogh Viktor, Nagy Angelika and Csanaky Szilvia Piroska* for their most appreciated work in data collection. Without their help, I would not have been able to write this thesis.

Whenever I use 'we' in my thesis, I therefore reflect to our shared efforts and all the contributions of the above mentioned colleagues.

I owe a lot to all of my fellow Ph.D. students, but especially to *Farkas Judit, Nagygyörgy Katalin, Mervó Barbara, Gyollai Ágoston* and *Gyepesi Áron*. I am lucky to call them not only colleagues but my friends as well, with whom we shared many joyful moments during our Ph.D. studies. Hereby, I wish them good luck in completing and successfully defending their thesis.

My colleagues at the drug outpatient centre of the Nyírő Gyula Hospital - National Institute of Psychiatry and Addictions, *Szabó Tünde, Dr. Winter Zsuzsanna, Dr. Rigó Péter, Fodor Kinga, Németh Mónika, Bene Katalin, Budavári Andrea, Sopuch Béláné Éva* and *Kostyál Kálmánné Jutka*

fill me with great energies during my day-by-day clinical practice with addicted patients. It is partly due to their love for life, sense of humour and strength that I love what I do.

I want to thank my parents, *Kapitány Ágnes* and *Gábor* for setting an example of humanity, kindness and togetherness, and also for inspiring me with their most valuable work in (mostly but not exclusively) sociological research. Their scientific versatility, the uniqueness of their research topics and their virtuous way of living had a great impact on my own thinking and values. I want to thank my brother*, Kapitány Mihály* and his wife, *Linda*, for the great moments we share. Being with them is a burnout-antidote.

I want to thank *Dr. Sulyok Mihály*, for being a trustful friend and also because I learned a lot from him about infectious diseases among injecting drug users.

Finally, I would like to thank my wife, *Dóri*, for all the support she provided in the past years. She has been and still giving me tremendous energies and encouragement. Furthermore, she not only gifted me with a wonderful baby, *Borika*, but also undertook the responsibility to attend the majority of parental duties in the past months, and thus gave me an opportunity to finish my thesis at full stretch. I want to thank both of them for making me balanced, even in the most burdensome life situations.

OWN PUBLICATIONS AS BASIS FOR THE THESIS

Three of the studies I am about to present in this thesis have already been published or accepted by the journal Human Psychopharmacology: Clinical and Experimental:

1. Kapitány-Fövény, M., Kertész, M., Winstock, A., Deluca, P., Corazza, O., Farkas, J., Zacher, G., Urbán, R., Demetrovics, Zs. (2013a). Substitutional potential of mephedrone: an analysis of the subjective effects. *Hum Psychopharmacol*, 28(4): 308-316. (*As basis for chapter 7.2.)*

2. Kapitány-Fövény, M., Mervó, B., Kertész, M., Corazza, O., Farkas, J., Kökönyei, Gy., Urbán, R., Demetrovics, Zs. (in press-a). Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone? *Human Psychopharmacology*, doi: 10.1002/hup.2490 (*As basis for chapter 7.3.)*

3. Kapitány-Fövény, M., Mervó, B., Corazza, O., Kökönyei, Gy., Farkas, J., Urbán, R., Zacher, G., Demetrovics, Zs. (in press-b). Enhancing sexual desire and experience: An investigation on the sexual correlates of gamma-hydroxybutyrate (GHB) use. *Human Psychopharmacology*, doi: 10.1002/hup.2491 (*As basis for chapter 7.6.)*

In the Foreword and Introduction parts of the thesis, I also cited some of the results of my further publications, including the following conference presentations:

4. Kapitány-Fövény, M. (2014). *Az új pszichoaktív szerek használóinak demográfiai és pszichológiai sajátosságai*. Új szerek – Új (kliens) utak? A Magyar Addiktológiai Társaság konferenciája, Budapest. 2014.03.27.-2014.03.28., p.1.

5. Kapitány-Fövény, M., Farkas, J., Csorba, J., Szabó, T., Demetrovics, Zs. (2013b). *Különbségek a szintetikus kannabinoidok és a kannabisz szubjektív hatásaiban, a használati mintázatban és a használat okaiban*. Magyar Addiktológiai Társaság IX. Országos Kongresszus, Siófok, 2013.11.21-2013.11.23., p. 25.

FOREWORD

As working in the field of both scientific research and clinical practice, I recurrently face the growing problem evoked by the rise of novel psychoactive substances (NPSs). Addicted patients started to consume chemicals with unknown psychoactive compounds, which resulted in severe withdrawal symptoms, menacer psychotic states, harmful and dangerous behavior to the public and to the individual as well. Literature often refers to NPS users as *human guinea pigs*, based on their habit of trying completely unidentified substances and therefore experimenting on themselves.

Experts of addiction care and research rapidly realized the relevance of NPSs and in recent years, an increasing number of addiction conferences thematically dealt with the topic of NPSs (e.g. Kapitány-Fövény, 2014). Although, it is now illegal to use the majority of these substances in Hungary and other parts of the world, users did not stop searching for further and further psychoactive substances.

As it is delineated by recent findings (e.g. Ledberg, 2015), temporarily legal status of NPSs is a highly appealing characteristic for their users, as interest in these substances often significantly decrease around or after the time of classification. In many cases, users purchase NPSs via online drug shops. Besides being a risk factor for easy availability, web-based marketing and internet interest on NPSs can also be used as a potential epidemiological indicator as well as a useful tool for testing theoretical assumptions about NPSs.

In my thesis I am dealing with two NPSs, mephedrone and GHB in depth. This choice is mainly explained by the morphosis of the Hungarian drug market and in connection to that, the conformation of the recreational scene. Clinical evidence and epidemiological data (Nemzeti Drog Fókuszpont, 2012) both suggest that in the past decade synthetic cathinones and GHB were the most popular NPSs in Hungary. Later on, synthetic cannabinoids began their triumph, and became the most frequently abused NPSs. Yet, I am not dealing with synthetic cannabinoids in my thesis for a practical reason: NPS market is characterized by its ever-changing face, with a novel substance appearing in every year or even month. If I deal with synthetic cannabinoids, then I need to deal with the next available NPS as well, including the most recently appeared Facebook-drug, which was first issued by the National Public Health and Medical Officer Service of Hungary in May 2015, and has already been covered by foreign press as well. And so on. I chose to do my

researches exclusively on cathinones and GHB in order not to lose focus. However, the study of synthetic cannabinoids is among my future research plans.

The studies included in my thesis had two main goals. As a first goal, I aimed to explore the characteristics of the first and current NPS use, including the social context of the use, the most frequently experienced subjective and somatic effects of mephedrone and GHB, and the psychiatric symptoms associated with their consumption. As part of this first goal, I also aimed to identify and test potential functions of the use of selected NPSs. In case of mephedrone, this function manifests itself in mephedrone's potential to be an effective substitute for not only MDMA and other psychostimulants but for opioids and other intravenously administered substances as well. Considering GHB, its main function is manifested by its role in human sexuality.

My second goal was to test the adaptability of three psychological etiological model in explaining NPS use: a) self-medication hypothesis, b) the impact of social context and c) the role of traumatic life events. When I hypothesized that users with more frequent or more intense (e.g. injecting) NPS use show elevated psychiatric symptom profiles (see chapter 7.3.), I mainly leaned on the basis of Khantzian's Self-Medication Hypothesis (SMH). When I assessed traumatic life events among opioid dependent patients (see chapter 7.4.), I presumed that those who abuse NPSs during their opioid substitution treatment show more intense emotional reactions to potential traumatic life events. And when I assessed social context of NPS use (see chapter 7.3. and chapter 7.6.), I emphasized the relevance of user's social environment regarding both the onset and persistence of NPS use.

INTRODUCTION

1. Transformation of illicit drug market

In the past decade, illicit drug market has markedly changed. With the growing popularity of web-based marketing and a decrease in the availability and purity of heroin, cocaine and ecstasy -accompanied by an increase in the price of these substances-, an era of NPSs arrived. A reduction in heroin's, cocaine's and ecstasy's availability was significant not only in Europe but in Australia (Mattick et al., 2004) as well. This change had an enhanced impact on the substance use patterns of participants in the contemporary injecting drug scene, such as the clients of needle exchange programs or the patients of various opioid-substitution therapies. Hypothesized causes of the shortages of these substances include altering conditions in source countries (e.g. a drop in opium production in Afghanistan, linked to poppy blight and unfavourable weather conditions leading to fungal infections), strategic changes among drug traffickers (e.g. a preference for easily producible synthetic products) and the success of increased interdiction efforts (Mattick et al., 2004; EMCDDA, 2011a).

NPSs are sometimes falsely identified with designer drugs, thus a conceptual clarification might be necessary, even if the majority of NPSs are truly designer drugs. Designer drugs are chemically altered compounds derived from previously banned substances with the primary goal to circumvent drug legislation. These chemicals are often called 'legal highs' for this reason. However, the term 'designer drug' was already in use during the 80s to describe such substances (e.g. Buchanan and Brown, 1988). Therefore, NPSs are interpreted and cited as 'novel' psychoactive substances within the confines of a current and rapidly changing time perspective in relation to already existing psychoactive substances. Between 2010 and 2012 the number of identified online shops, selling NPSs as products not intended for human consumption – such as bath salts, plant fertilizers or research chemicals – increased from 170 to 693 (EMCDDA, 2012). The majority of these web shops were based in the Netherlands (38 online shops), the United Kingdom (20 online shops) and Germany (20 online shops). In Poland, France and Hungary more than 5 web shops were located in 2010 (EMCDDA, 2011a). At present, illegitimate users still have the opportunity to order NPSs via online drug shops, even with an option of home delivery. Web-based marketing is considered to be a high risk factor regarding easy availability and uncontrolled drug trafficking. Personal interaction with a dealer is no longer a necessary requirement of

obtaining the chosen psychoactive substance, web-based distribution of NPSs became an appealing solution for overcoming this burden for habitants of not only major cities but smaller towns and villages as well. Relative anonymity and perceived personal safety are further factors that make online purchasing an engaging option (Dick and Torrance, 2010).

Currently there are more than 450 NPSs being monitored by the EMCDDA with more than 100 NPSs reported for the first time in 2014 (EMCDDA, 2015), indicating that the market is still intensely transforming. Prevalence rate of the use of NPSs overpass that of "classic" psychoactive substances such as ecstasy or speed. Nevertheless, one should keep in mind that prevalence rates regarding the use of NPSs are often based on seizure data or studies examining non-representative samples, therefore we should rather consider these result as minimum estimates due to the lack of standardised measures. Between 2008 and 2013 a seven-fold increase in the number of NPS seizures was reported across Europe (EMCDDA, 2015). The majority of seized substances were either cathinones, such as mephedrone (*4-methylmethcathinone*), pentedrone (*2-(methylamino)-1-phenylpentan-1-one*), methylone (*3,4-methylenedioxy-N-methylcathinone*), 4-MEC (*4-methylethcathinone*) and MDPV (*3,4-methylenedioxypyrovalerone*), or more recently synthetic cannabinoids, such as JWH-type products (e.g. JWH-018: (*1-pentyl-3-(1-naphthoyl)indole*, named after John William Huffman, a professor of organic chemistry who first synthesized cannabinoids).

A significant number of the most popular NPSs are psychostimulants, indicating that the absence or shortage of popular club drugs, such as MDMA, resulted in an increased need for novel recreational substances in the party scene. With regard to GHB (*gamma-hydroxybutyrate*) and its precursor, GBL (*gamma-butyrolactone*), we might consider their emerging popularity as a renascible trend of their consumption during the 2000s (EMCDDA, 2008) and classify them as NPSs by their novatory reputation among recreational drug users. In this context, the term 'novel' refer to recent and increased availability of these drugs.

As my thesis primarily focus on mephedrone and other cathinones as well as on GHB, I will provide further information about these substances in the following. Examining synthetic cannabinoids – as most recent NPSs – is one of my future research goal (see chapter 8.2.1.).

1.1. Mephedrone and other cathinones

The first online reports about mephedrone occurred in 2003 (Power, 2009); however, in that time, it was mainly purchased via online drug shops (e.g. Roussel et al., 2009; Camilleri et al., 2010). Its popularity as a commonly abused substance, started to spread in the recreational drug scene only after 2007 (Psychonaut Web Mapping Research Group, 2009). The growing popularity of mephedrone can be attributed to the wide availability of this substance because of the globalisation of the Internet and web-based marketing. Another possible reason for mephedrone's popularity is that—according to users' reports—it can give a better quality high, than other stimulants (e.g. Winstock and Mitcheson, 2010). Furthermore, mephedrone's popularity increased when MDMA's and cocaine's purity fell (e.g. EMCDDA, 2011a; Schneider and Meys, 2011; Sindicich et al., 2011), and/or when the availability of MDMA decreased (EMCDDA, 2010; e.g. Brunt et al., 2011). Followed by its ban in all the EU member states (e.g. in Hungary it was banned in January 2011) mephedrone was replaced with other cathinones such as MDPV and later pentedrone.

In comparison to mephedrone and other cathinones, MDPV contains a pyrrolidine ring in its chemical structure, which gives MDPV potent actions, blocking the uptake at dopamine and norepinephrine transporters (Marusich et al., 2014). In some studies (Cameron et al., 2013), MDPV was found to be more potent than cocaine, with longer lasting effects as well. Users often call it 'MP4' or 'music' as street names of this substance. 4-MEC, a 'second-generation' mephedrone analog, also became popular after the legislative ban on mephedrone. 4-MEC produce large increases in extracellular 5-HT (*5-hydroxytryptamine: serotonin*) (Saha et al., 2015), however, alongside with methylone, it was found to be less potent than other cathinones (Araújo et al., 2015). After the zenith of mephedrone's and MDPV's popularity, pentedrone became the most frequently abused cathinone, cited as 'crystal' or 'penta crystal' by illegitimate users. It acts as a reuptake inhibitor for dopamine and norepinephrine, the same mechanism of action as methylphenidate (Simmler et al., 2014), the chemical compound of ADHD-medication: Ritalin and Concerta.

Cathinone-derivatives are mainly marketed as bath salts and plant fertilizers (not for human consumption). Mephedrone is considered to be the prototype of cathinones, also the most popular among these NPSs, therefore during my empirical researches (see chapter 7.1., chapter 7.2. and

chapter 7.3.), I primarily focused on mephedrone and only partially on other cathinones (see chapter 7.4.).

User characteristics

Users of NPSs often constitute a hidden subpopulation, which is hard to reach in terms of both research and treatment. Existing research, however, help in describing this population with regard to its main sociodemographic charachteristics. Mephedrone users are recurrently found to be males as a majority (Winstock and Marsden, 2010; Winstock et al., 2010; Carhart-Harris et al., 2011; Lea et al. 2011), mostly in their twenties (Winstock and Marsden, 2010; Winstock et al., 2010; Carhart-Harris et al., 2011; Lea et al., 2011; Winstock et al., 2011b). Considering their educational level, available data suggest that users often have a completed high school or even a college/university degree (e.g. Dargan et al., 2010; Lea et al., 2011).

Regarding co-ingested substances, MDMA, amphetamines, cocaine, ethanol and cannabis are most frequently mentioned concomitantly used drugs (Newcombe, 2009; Matthews and Bruno, 2010; Winstock et al., 2011b).

1.2. GHB

GHB, a naturally occurring compound of mammalian central nervous system and peripheral tissue (Bessman and Fishbein, 1963; Roth, 1970; Mamelak, 1989; Tunnicliff, 1992), and as such cannot be labeled as a designer drug, was first synthesized by Henri Laborit in 1960 (Laborit et al, 1960). Since then, GHB has been used as a general anesthetic and sedative in the treatment of narcolepsy (e.g. Broughton and Mamelak, 1979; Scharf et al., 1985; Mamelak et al., 1986; Scrima et al., 1990; Lammers et al., 1993), alcohol- (e.g. Gallimberti et al., 1989; Gallimberti et al., 1992; Nimmerrichter et al., 2002; Korninger et al., 2003; Nava et al., 2007) and opiate withdrawal syndrome and dependence (Gallimberti et al., 1993; Gallimberti et al., 1994; Rosen et al., 1997). Abuse liability of this chemical and the presence of a possible GHB dependence was empirically demonstrated (e.g. Galloway et al., 1997; Gonzalez and Nutt, 2005; Caputo et al., 2009).

Athletes and body-builders started to use GHB (or its precursor, GBL) in the 1980's (e.g. Michael and Hall, 1994) in order to improve their performance, as GHB may even double the secretion of growth hormone (Galloway et al., 1997; Van Cauter et al., 1997). Widespread use of this substance as a recreational drug began in the 1990's (Galloway et al., 1997; Kam and Yoong,

1998; Nicholson and Balster, 2001) and according to some more recent studies conducted in dance music settings, and in homosexual subpopulations, GHB is still popular recerational substance (McDowell, 2000; Mansergh et al., 2001; Mattison et al., 2001; Bellis et al., 2002; Nabben et al., 2006; Palamar and Halkitis, 2006; Halkitis et al., 2007; Hillebrand et al., 2008). Despite its remarkable history both as a medication and an illicit substance, GHB is also considered to be an NPS as its popularity among recreational drug users arose in the 2000s, especially in Hungary, where it is frequently referred by its street name, Gina.

User characteristics

As former studies highlight, GHB users are most typically young adults in their twenties (e.g. Miotto et al., 2001; Degenhardt et al., 2003; Sumnall et al., 2008; Brunt et al., 2013; Wisselink et al., 2013) or early thirties (e.g. Barker et al., 2007; Lee and Levounis, 2008; Oliveto et al., 2010; Stein et al., 2011), and the vast majority - approximately two thirds or more of them - are reported to be males (e.g. Miotto et al., 2001; Lee and Levounis, 2008; Sumnall et al., 2008; Stein et al., 2011; Brunt et al., 2013; Wisselink et al., 2013). Considering their educational background and living conditions, mixed results were published, as GHB users were presented to have low education level and a high rate of unemployment by some papers (e.g. Brunt et al., 2013), while other studies reported that well-educated people with stable employment and moderately high income (Degenhardt et al., 2003; Barker et al., 2007; Lee and Levounis, 2008) are also found among them.

GHB is frequently co-ingested with ethanol, MDMA, amphetamines, cocaine, cannabis and sometimes with opioids (Rosen et al., 1997; Miotto et al., 2001; Sumnall et al., 2008; Brunt et al., 2013). In terms of research, GHB users are usually reached at emergency deparments (McDonough et al., 2004) as a significant proportion of these users do not seek treatment.

2. POPULARITY OF NPSs

2.1. Epidemiology

2.1.1. Cathinones

Based on the results of the few published general population studies in which mephedrone was included, in 2010-2011 the last year prevalence of mephedrone use was 1.4% in England and Wales – a level similar to that of ecstasy – (Smith and Flatley, 2011), 1% in Northern Ireland where lifetime prevalence was 2% (NACD and PHIRB, 2011). Mephedrone was also one of the most frequently seized synthetic substance in this period in Hungary and in the UK as well. For instance, in Northern Ireland the number of mephedrone seizures was even higher than the number of ecstasy seizures in 2009/2010 (Davies et al., 2010). According to the paper of Brunt and his colleagues (2011), in the Netherlands, starting from 2009, mephedrone was the only cathinone derivative found in tablets sold as ecstasy. In 2009, 11.5% of the total amount of ecstasy tablets exclusively contained mephedrone.

Naturally much higher prevalence rates were found among recreational drug users and club goers. Mixmag's internet surveys among UK clubbers estimated a 40% lifetime use of mephedrone in 2010 (Dick and Torrance, 2010) and 61% in 2011 (Winstock, 2011), although last month use of this substance fell from 33% to 25%. In 2012, Mixmag's and Guardian's common drug survey (Winstock, 2012) reached 15500 respondents from 33 countries but mainly from the UK (N=7700) and the USA (N=3360). Lifetime prevalence of mephedrone use was 42.7% in the UK, last year prevalence was 19.5% among UK respondents and 30% among UK regular clubbers but only 2% among US respondents. In Italy, lifetime prevalence of mephedrone in the club scene of Rome was 18.8% in 2013 (Vento et al., 2014).

Regarding Hungary, prevalence rates of mephedrone use are available only among adolescents as no general population study has studied its epidemiology. In the latest ESPAD (European School Survey Project on Alcohol and Other Drugs) study, lifetime prevalence of mephedrone use was found to be 6% (Elekes, 2012), a rate that was higher than lifetime consumption of amphetamine-derivatives or MDMA.

2.1.2. GHB

Available data on GHB prevalence in general population include a 0.4% last year and 0.2% past month prevalence rate in the Netherlands in 2009 (van Laar et al., 2012), a 0.1% last year prevalence in the United Kingdom in 2011/2012 (UK Home Office, 2012), a 0.5% lifetime and 0.1% last month prevalence in Australia in 2004 (Degenhardt and Dunn, 2008) and a 0.2% lifetime prevalence in Hungary in 2007 (Paksi et al., 2009). Nevertheless, further indicators highlight GHB's and GBL's problematic use, which was rapidly increasing in recent years, especially in the European Union. For instance, in the Netherlands, the number of GHB intoxications increased from 300 to 1200 between 2004 and 2009 (van Laar et al., 2012). In the United Kingdom a similar increase was observable, as the number of individuals reporting the use of GHB increased from 158 to 270 between 2006 and 2010, among those presented to emergency departments (Wood et al., 2013).

Among club attendees, much higher prevalence rates were explored, just like in the case of mephedrone. In the United States, as a result of stratified analysis (stratifying by gender and sexual orientation), GHB's lifetime prevalence was found to be the highest among gay/bisexual male club-goers (15.1%) in comparison to heterosexual men (11.7%) and women (7.2%) and lesbian/bisexual females (9.2%) (Kelly et al., 2006). More recently, past four month prevalence of GHB use was reported to be 5% among club-goers in New York City (Ramo et al., 2010). Lifetime prevalence of GHB use was 5.9% among Hungarian attendees of electronic parties (Demetrovics, 2005), while among Italian club-goers, lifetime prevalence of GHB use was 10.2% (Vento et al., 2014).

Among adolescents in Hungary, GHB was not as frequently consumed as mephedrone. Based on the results of the previously mentioned ESPAD study, the lifetime prevalence of GHB use was 2.5%, a same rate as cocaine's lifetime prevalence (Elekes, 2012).

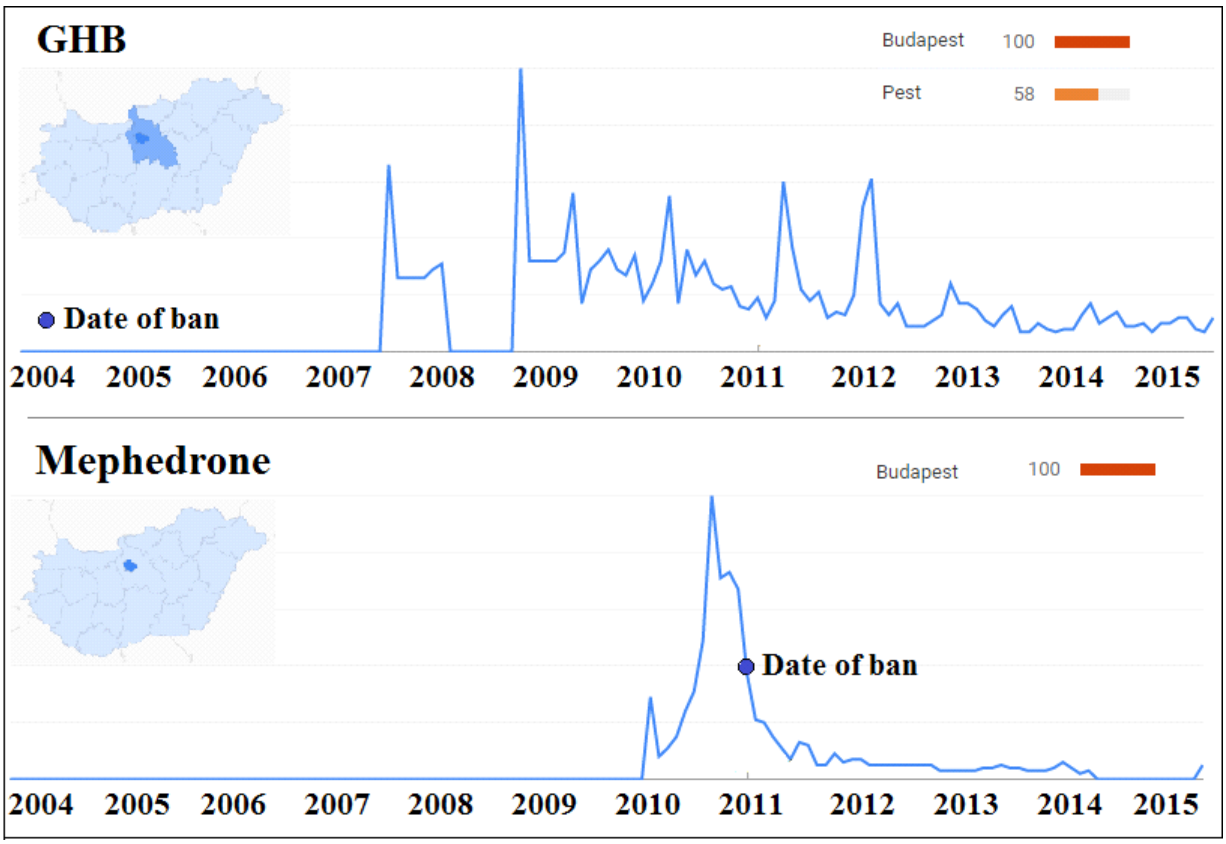
2.1.3. Web search queries as potential epidemiological indicators

With widespread availability of the internet, both drug users and traffickers started to obtain information about NPSs via online platforms, such as chat-rooms or various fora (Smith and Garlich, 2013). Internet became the primary source of illicit drug information, especially among adolescents and young adults (European Commission, 2008). Effective dissemination of NPS information is further supported by networking sites for *psychonauts* (i.e. persons who experiment with mind-altering psychoactive substances), such as Erowid, Dancesafe, Bluelight, Lycaeum (Smith and Garlich, 2013) or DAATH in Hungary (Móró and Rácz, 2013). This new pattern of collecting NPS-related information as well as the phenomenon of ordering drugs via online drug shops brought a novel epidemiological method into being: web search queries were found to be useful tools in predicting the prevalence of drug use and related harms. The rate of web search queries may reflect various interests of a social network.

Changes in the trends of web search queries regarding certain search terms provided by Google Trends, Google Flu Trends or Google Dengue Trends have already been utilized for detecting the epidemics of various infectious diseases, such as influenza (Ginsberg et al., 2009), ebola (Milinovich et al., 2015), dengue (Chan et al., 2011) or AIDS (Zhou et al., 2010). However, with regard to the analysis of specific characteristics and epidemiology of substance abuse, this method is not yet as common. Among the few examples, one study has explored possible effects of codeine-containing medication sales restrictions on public interest in the production and use of krokodil (desomorphine) as an NPS (Zheluk et al., 2014). Another study examined the impact of online news reported fatal mephedrone-overdoses on the web interest in buying mephedrone (Forsyth, 2012). Overlaps between synthetic cannabinoid legislation, media and drug-related harms were also assessed (Bright et al., 2013) by using this novel method as well as the estimation of cannabis prevalence across distinct regions (Steppan et al., 2013). Only one study has dealt with toxicological correlates of web search query data (Yin and Ho, 2012), resulted in high correlation between the number of cases of exposures to ”bath salts” reported by US poison centers and internet searches for ”bath salts”.

In Hungary, the overview of web search queries between 2004 (first year of available Google Trend data) and the present day (May 2015), regarding ’GHB’ and ’mephedrone’ as search terms, results in the folowing figures (Figure 1):

Figure 1. Web search queries with search terms ’GHB’ and ‘mephedrone’: Hungary (2004-2015)



As Google Trends search results demonstrate, web search queries regarding both GHB and mephedrone were located in either Budapest or Pest County. In case of GHB, which was banned in 2004, fluctuation in search queries show no connection with the date of ban. With regard to mephedrone, search queries show a relevant drop after the date of ban (January, 2011). Further and detailed statistical analysis regarding the connection between illegal status of these substances and the rate in web search queries will be presented among the results of my empirical researches (7.1. section of the thesis).

2.2. Reasons of NPS use

Online availability of not only designer drugs but information about these psychoactive substances have led to severe public health challenge (Corazza et al., 2014) and also to the trend of producing drugs at home, as in the case of desomorphine – more frequently labeled as krokodil - (Booth, 2013; Harris, 2013), cathinones (often cited as 'Boltushka' in this form) and opiates (Van Hout, 2014). The growing number of online drug shops, the new trend of home-production and the relatively cheap price of these substances increased the availability of designer drugs. Therefore, the popularity of designer drugs is principally explained by practical or even economical aspects of their use, such as the temporary absence of legal risks, the low cost of these substances, their easy availability via the internet (Cottencin et al., 2014), their attractive, multicolored packaging and exotic brand names, or the fact that they are often not easily detectable in urine and blood samples (Fattore and Fratta, 2011). Presumed purity of designer drugs can also be mentioned as one of their main benefits for users. As an example, despite different physical characteristics of various synthetic cannabinoid products, definitely high purities (range between 75% and 100%) of JWH-018 and JWH-073 were found (Ginsburg et al., 2012), although it is also addressed that the more severe withdrawal syndrome of synthetic cannabinoids in comparison to cannabis could be due to the fact that these synthetic products may contain heterogeneous compounds such as amphetamine-like substances (Nacca et al., 2013) or even synthetic opioids, like O-desmethyltramadol (Dresen et al., 2010). Pharmacokinetical characteristics of designer drugs also increase their reputation among illegitimate users. For instance, in case of cathinones, high blood-brain barrier permeability of especially mephedrone and MDPV was proven in an in vitro model (Simmler et al., 2013), whereas increased reinforcer efficacy and abuse liability of methylone was found by employing intravenous self-administration and intracranial self-stimulation in rats (Watterson et al., 2012). Yet, research regarding synthetic cathinone pharmacokinetics in humans is lacking.

As a further example of assessing NPS use reasons, in confines of a qualitative study, we interviewed ten male Substance Use Disorder (SUD) patients with a history of both cannabis and synthetic cannabinoid consumption, regarding their motivations of choosing either cannabis or synthetic cannabinoids (Kapitány-Fövény et al., 2013b). Most frequently reported reasons of using synthetic cannabinoids were 1) shorter effect duration (between 10 minutes and 1 hour), 2) low price (usually around 500 HUF~1.6 EURO/gramme, which is approximately one-fifth of the price

of cannabis), 3) easy availability (online purchase and home-production) and 4) more intense, stimulant-like effects. Two of these patients additionally reported that they consider synthetic cannabinoids to be more safe, because its street name is *bio-weed* or *herbal*, which induces a false illusion of synthetic cannabinoids being natural substances and also a decreased risk perception about the potential dangers of synthetic cannabinoid consumption.

Still, the primary explanation for designer drugs' popularity may be their potential to substitute formerly banned psychoactive substances. Mephedrone was found to be an effective substitute of mainly MDMA (Brunt et al., 2011; Carhart-Harris et al., 2011; Winstock et al., 2011a; Kapitány-Fövény et al., 2013a), GHB is often consumed as an alternative of alcohol (Johnson and Griffiths, 2013), while a vast number of cannabis users switched to smoking synthetic cannabinoids (e.g. Winstock and Barratt, 2013; Gunderson et al., 2014).

3. FUNCTIONS OF NPS USE

Substance use in general bears many potential functions, including stress reduction (Hyman and Sinha, 2009), pain management (Manchikanti et al., 2006), mood altering (Boys et al., 1999) or the experience of an altered state of consciousness (McPeake et al., 1991) which often satisfies spiritual needs (Heinz et al., 2010). In dysfunctional families, substance use of the child may evoke solidarity between the parents who are otherwise occupied with their relationship problems (Demetrovics, 2007). Therefore substance use may detract parents' attention from these difficulties and as such, it can also create a fragile but temporarily adaptive balance in the family.

In case of the NPSs studied in my thesis, cathinones and GHB, the literature highlights two major functions of these substances. Mephedrone and other cathinones are considered to be effective substitutes for MDMA and other entactogenic stimulants– with psychopharmacological effects that facilitate interpersonal activities and induce feelings of connectedness with others – (see chapter 3.1.1.) and also for intravenously administered substances, including opioids (see 3.1.2.). The main functions of GHB use are linked to human sexuality (see chapter 3.2.1. and chapter 3.2.2.), both as a potential date-rape drug and a potent aphrodisiac. In what follows, I present the above mentioned functionalities of NPS use in depth.

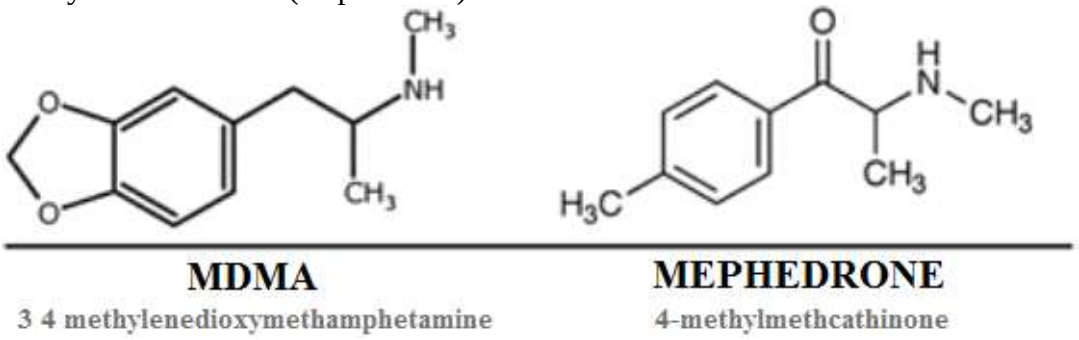
3.1. Substituting other substances

3.1.1. Mephedrone and MDMA

The psychological effects of 3,4-methylenedioxy-methamphetamine (MDMA) were first reported by Shulgin and Nichols (1978); and in the next three decades, several studies investigated the main psychological and somatic effects of MDMA and other entactogens (e.g. Downing, 1986; Peroutka et al.,1988; Solowij et al., 1992; Hermle et al., 1993; Davison and Parrott, 1997; Parrott and Lasky, 1998; Parrott et al., 1998; Vollenweider et al., 1998). According to these studies, MDMA's main effects include positive mood states (e.g. euphoria, inner contentment, feelings of ease, energy, happiness, exhilaration, confidence, open-mindedness or relaxation), entactogenic effects (e.g. closeness to others, feeling of intimacy, increased empathy, talkativeness or friendliness), psychedelic effects (e.g. increased perception, distorted vision, visual or auditory hallucinations) and adverse physiological and psychological effects partly as side effects of the sympathomimetic effects, (e.g. bruxism, muscle tension etc.) and partly as typical comedown symptoms (e.g. fatigue, lack of appetite, palpitations, sweating, nausea, weakness, insomnia,

bruxism, paranoia, lethargy, anxiety and depression). Following the classification of MDMA as an illicit substance, a great number of synthetic and nonsynthetic substances have appeared on the recreational drug market as potential substitutes for MDMA but none of them reached or even approached the popularity of ecstasy (MDMA). Mephedrone, however, is the first substance in the past two decades that quickly gained a constant position on the illegal drug market. Mephedrone, as a stimulant substance, is often compared with other stimulants, such as ecstasy, amphetamine or cocaine (e.g. Schifano et al., 2010). Regarding its chemical structure, mephedrone is a congener of methcathinone and cathinone, which can be identified in the khat plant - *Catha edulis* -, which has been chewed for its euphoric and mild stimulant effects dates back many centuries as well as today, mainly in Somalia, Yemen, Kenya and Ethiopia (Kalix, 1992) (Figure 2).

Figure 2. Chemical structures of 3,4-methylenedioxymethamphetamine (MDMA) and 4-methylmethcathinone (mephedrone)



In recent years, some studies examined the typical subjective and somatic effects of mephedrone (Newcombe, 2009; Psychonaut Web Mapping Research Group, 2009; Dargan et al., 2010; Winstock and Marsden, 2010; Brunt et al., 2011; Winstock et al.,2011a, 2011b; Freeman et al., 2012), as well as the characteristics of its use (Winstock et al., 2010; Lea et al., 2011). Table 1 lists all the desired and unwanted effects of mephedrone reported by the empirical studies of this issue. Mephedrone mainly induces entactogen effects; and just like MDMA, it may induce possible unwanted adverse somatic effects. However, pleasant psychological effects can overwrite the experience of these negative bodily symptoms, leading the user on to perceive his or her substance use in a pleasant or affirmative way (Table 1).

Table 1. Reported desired and unwanted subjective and somatic effects of mephedrone

Somatic		Psychological	
Desired effects	**Unwanted adverse effects**	**Desired effects**	**Unwanted adverse effects**
Increased energy	Nose-burns, nose-bleeds	Euphoria	Blurred vision
	Head rushes	Friendliness	Delusions
	Dilated pupils (Mydriasis)	Hallucinations	Inebriation
	Dry mouth	Enhanced empathy	Aggression
	Hot flushes / Overheating / Increase in body temperature	Talkativeness	Cravings
	Tachycardia	Stimulation	Nightmares
	Muscular tension	Intensification of sensory experience stimulation	Insomnia / Hard to sleep
	Bruxism/Jaw clench	Increased sexual desire, stimulation	Fatigue
	Suppressed appetite	Mood enhancement	Loss of concentration/ Memory problems
	Nausea / Vomiting	Decreased hostility	Anxiety
	Shrunken testicles	Increased insight	Paranoia
	Respiratory difficulties	Improved concentration	Dysphoria
	Influenza like symptoms	Urge to move	Depression
	Dermatitis like symptoms	High self-confidence	Addiction
	Numbness	Increased alertness	Panic
	Painful, discoloured joints, extremities, skin		Agitation
	Nystagmus		Buzzing
	Painful nasal drip, sore nasal passages		Altered time perception
	Dizziness		Confusion
	Headaches		Lethargy
	Tremors, palpitations		
	Burns		
	Body sweats		
	Chest pain		
	Skin rash		

Note: Effects are collected out of the following studies: Newcombe (2009); Psychonaut Web Mapping Research Group (2009); Dargan et al. (2010); Winstock and Marsden (2010); Brunt et al. (2011); Winstock et al. (2011a); Winstock et al. (2011b); Freeman et al. (2012)

Even though some studies have dealt with the differences and similarities between MDMA and mephedrone (Brunt et al., 2011; Carhart-Harris et al., 2011; Winstock et al., 2011b), none of them examined directly the potential role of mephedrone as an effective substitute for entactogens, such as MDMA.

3.1.2. Mephedrone and opioids

In the new era of NPSs, opioid-dependent patients also started to substitute missing heroin and other opioids primarily and for a longer period with cathinones. Around 2010 and 2011, cathinone-derivatives, such as mephedrone, pentedrone, methylone, 4-MEC and MDPV were federally controlled worldwide – for instance, by the Council Decision of 2 December 2010, mephedrone was submitted to control measures in EU Member States - and no longer categorised as a legal high. Nevertheless, users' perceptions of the safety of these substances were not affected by their once-legal status and cathinones such as mephedrone were still widely available months after the ban (McElrath and O'Neill, 2011), whereas some designer drugs, such as synthetic cannabinoids, are still, however falsely, perceived as safe drugs, partly due to their advertisement describing them as natural herbs or harmless incense blend (Fattore and Fratta, 2011).

A transition to injecting cathinones instead of or concomitantly to intravenous opioid use is an other characteristic of the designer drug scene related to the markedly changed drug market. High frequencies of injecting cathinone use were found among clients of needle exchange programs (e.g. Csák et al., 2013; Péterfi et al., 2014) and other low threshold harm reduction services (Van Hout and Bingham, 2012). The trend of cathinone injecting, however is rapidly forming. Following its decreasing popularity, mephedrone was first substituted with MDPV and then with pentedrone (Péterfi et al., 2014), while treatment seeking opioid-dependent users started to abuse new and basically unknown cathinones instead of heroin or methadone as a form of relapse.

Recently, a number of studies have examined the characteristics of mephedrone use including the frequency of use, the route of administration, the ways users usually purchase this substance, and the typical amount of mephedrone consumed (Dargan et al., 2010; Matthews and Bruno, 2010; Carhart-Harris et al, 2011; Lea et al., 2011; Winstock et al., 2011a; Winstock et al., 2011b). Based on these results, injecting as a form of use was not common (Table 2).

Table 2. Reported frequency, route-, forms-, amount and source of mephedrone use

	Dargan et al, 2010 (N=205)	Matthews and Bruno, 2010 (N=146)	Carhart-Harris et al, 2011 (N=1506)	Lea et al, 2011 (N=23)	Winstock et al., 2011a (N=947)	Winstock et al., 2011b (N=100)
Frequency of use (%)						
On one occasion	**23.4**	n.s.d.	n.s.d.	n.s.d.	n.s.d.	n.s.d.
Occasional use/ Monthly or less often	**41.5**	n.s.d.	n.s.d.	n.s.d.	**69.7**	n.s.d.
Weekly use or more often	**30.7**	n.s.d.	n.s.d.	n.s.d.	**15.1**	n.s.d.
Daily use	**4.4**	n.s.d.	n.s.d.	n.s.d.	n.s.d.	n.s.d.
Last mephedrone use (%)						
Over 1 year ago	n.s.d.	n.s.d.	n.s.d.	**30.4**	n.s.d.	n.s.d.
Last year	n.s.d.	n.s.d.	n.s.d.	**17.4**	**93.9**	n.s.d.
Past 6 months	n.s.d.	**80.8**	n.s.d.	**17.4**	n.s.d.	n.s.d.
Past month	n.s.d.	n.s.d.	n.s.d.	**34.8**	**80.5**	n.s.d.
Route of administration (%)						
Sniffing/Snorting	n.s.d.	**64**	**57**	**34.8**	**65.9**	**79**
Oral	n.s.d.	**67**	**28**	**26.1**	**34.1**	**9.9**
Intravenous	n.s.d.	**1**	**3**	**0**	**0**	**0**
Smoking	n.s.d.	**4**	n.s.d.	n.s.d.	n.s.d.	**0**
Other form	n.s.d.	n.s.d.	n.s.d.	n.s.d.	n.s.d.	n.s.d.
Anal insertion	n.s.d.	**0**	**0**	**4.3**	**0**	**0**
Context of mephedrone use (%)						
At friends' home or at home with friends	n.s.d.	n.s.d.	n.s.d.	**34.8**	n.s.d.	n.s.d.
At bars/clubs (both straight and homosexual)	n.s.d.	n.s.d.	n.s.d.	**52.2**	n.s.d.	n.s.d.
Dance parties/ house parties	n.s.d.	n.s.d.	n.s.d.	**13**	n.s.d.	n.s.d.
Sex parties	n.s.d.	n.s.d.	n.s.d.	**4.3**	n.s.d.	n.s.d.
At home (alone)	n.s.d.	n.s.d.	n.s.d.	**8.7**	n.s.d.	n.s.d.
Average dosage of mephedrone consumed (mg)	n.s.d.	n.s.d	**500 mg (25%) <500mg (28%) >500 mg (39%)**	**1 'bump' to 1000 mg**	**500-1000 mg**	**1000 mg (IQR= 250-1275 mg)**

Nevertheless, these studies did not explore the phenomenon of intravenous mephedrone use in depth. Some initial qualitative evidence has been presented in the study of Van Hout and Bingham (2012), which presents self-reports of mephedrone injectors. This study, however, did not present any data on the differences between injectors and noninjectors. The need for the examination of the injecting sub-population of mephedrone users is supported by some earlier warnings (Rácz et al., 2012; Kapitány-Fövény et al., 2013a; Péterfi et al., 2014).

3.2. GHB and sexuality

GHB's impact on human sexual behavior is linked to either unintentional GHB intake (drug facilitated sexual assaults) or intentional and mainly recreational GHB use.

3.2.1. Drug facilitated sexual assaults

Regarding GHB and other depressants that are often labeled as a 'roofie', the misuse of GHB as a potential 'date-rape drug' provoked the widest media and societal interest (Jansen and Theron, 2006; Karila et al., 2009). Studies examining this phenomenon resulted in various and often contradictory conclusions (e.g. Scott-Ham and Burton, 2005; Du Mont et al., 2010). Beside, professionals suggest to use the neutral term of 'alleged sexual assault' rather than 'date-rape' for several reasons (Németh et al., 2010), and they also emphasize the potential implications of GHB as well as other substances (i.e. alcohol, ecstasy, flunitrazepam, ketamine and marijuana) which may also be linked to such drug facilitated sexual assaults (Anglin et al., 1997; Merle, 1997; Simmons and Cupp, 1998; Woods and Winger, 1997, Scott-Ham and Burton, 2005; Jansen and Theron, 2006; Du Mont et al., 2010). According to a systematic review by Németh and colleagues (2010) on the involvement of GHB in sexual assaults reported by 11 articles between 1961 and 2009, this substance was detected in 0.2-4.4% of all reported sexual assaults. Even though this number might be an underestimation due to some specific factors (Németh et al., 2010), authors concluded that media reports about GHB-involved sexual assaults might be over-sensitive and misleading as they turn attention away from other substances, which may also play a more relevant and more frequent role in these crimes. Nevertheless, due to the specific disinhibitory effect of GHB (Laborit, 1972), the relationship between its use and sexuality remained a diffuse research topic.

3.2.2. Sexual correlates of intentional GHB use

As the first one to describe, Laborit identified four sexual-enhancing effects of GHB: disinhibition, heightened sense of touch (i.e. increase in tactile sensitivity), enhancement of male erectile capacity and more intense orgasm (Laborit, 1972). In the past decades mainly qualitative or observational studies have dealt with or mentioned the sexual correlates of the intentional and mainly recreational use of GHB (Laborit, 1972; Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008). However, the few quantitative studies (Miotto et al., 2001; Sumnall et al., 2008; Stein et al., 2011) have not specifically assessed the sexual effects of GHB use. Table 3 presents the findings of former studies regarding GHB's effect on human sexuality. Gender differences in GHB's sexual effects also remained understudied, although Laborit (1972) emphasized that primarily males experience these sexual-enhancing effects of this substance.

GHB's effects, and especially its ability to decrease social inhibitions, may also promote high risk sexual behaviors associated with increased probability of HIV infection (Romanelli et al., 2003), mostly among gay and bisexual men who attend clubs. The relation between sexual orientation and more frequent and severe substance use is usually moderated by stress markers, attachment style and maternal affection as well (Rosario et al., 2014).

Table 3. Reported sexual effects and correlates of GHB use

Direct wanted sexual effects	**Direct adverse sexual effects**	**Sexual enhancement among typical reasons of GHB use?**	**Risky sexual behavioral correlates**
Increased sexual desire or arousal [b,c,d,e,f]	Orgasm is more difficult to achieve [f]	No data [a,c,d,e]	Possibility of heightened sexual risk-taking [d]
Disinhibition [a,b,c,d,e]	Harder to remain physiologically stimulated during sex [f]	Mentioned [b,f,g]	Greater willingness to engage in sexual activity [d]
Increased intensity or new quality of orgasm [a,b,c,f]	Disinhibition [f]		Greater risk of unsafe sex [e]
Heightened sense of touch (tactility) [a,b,d,f]			
Increased sexual intimacy or psychological and social connection [d,f]			
Enhancement of male erectile capacity [a]			
Increased attraction to others[c]			
Dependence on GHB for sex[e]			

[a]Laborit, 1972; [b]Miotto et al., 2001; [c]Palamar and Halkitis, 2006; [d]Barker et al., 2007; [e]Lee and Levounis, 2008; [f]Sumnall et al., 2008; [g]Stein et al., 2011

4. ETIOLOGY

In this thesis, I emphasize the relevance of three psychological etiological models: 1) the self-medication hypothesis; 2) the role of traumatic life events and 3) the impact of the social environment, as these models are considered to be of high importance not only in empirical research, but regarding the clinical field as well. These models constitute the theoretical framework for my empirical researches. As already mentioned before in the Foreword section, the second goal of my thesis was to test adaptability of these models in case of the use of the studied NPSs.

4.1. Self-medication hypothesis

Edward J. Khantzian's Self-Medication Hypothesis is one of the most frequently cited psychodynamic model of substance abuse. Khantzian formulated his original theory on the basis of clinical observations of heroin-dependent patients (Khantzian, 1975). Later on, he broadened his hypothesis and applied it to cocaine and alcohol users (Khantzian et al., 1990) and finally to SUD patients in general (Khantzian, 1999). Self-medication hypothesis suggests that substance use behaviors can be interpreted as self-regulation efforts in coping with intolerable affects, self-esteem problems or with difficulties in relationships and self-care. Therefore, as Khantzian states, individuals use and become dependent upon specific substances because they successfully relieve distress. Based on this model, individual preference for specific substances, which are often labeled as 'drug of choices', is primarily influenced by the psychopharmacological characteristics of these substances. Thus, different class of psychoactive substances may help in relieving different type of adverse states. Central Nervous System (CNS) depressants, such as opioids, barbiturates, benzodiazepines, alcohol or GHB, may create an illusion or temporary state of relief from tormenting feelings of isolation, emptiness, anxiety, anger and fear of intense closeness or dependency by softening rigid psychological defense mechanisms. CNS stimulants, such as cocaine, nicotine, amphetamine-derivatives or NPSs like cathinones, pyrovalerones (i.e. cathinones with a pyrrolidine group in their chemical structure) or piperidines, may counteract hyperactivity and inattention in cases of Attention-Deficit Hyperactivity Disorder (ADHD) (Wilens et al., 2007) or help in temporarily balancing emotional instability, low self-esteem, boredom or the lack of energy.

The causal controversy within the theory, including the bilateral relationship between psychopathology and substance use (i.e. comorbid disorders), has been critizised by others (e.g.

Frances, 1997), emphasizing that psychiatric symptoms and disorders (for details, see: chapter 5.1.) can be both causes and consequences of substance use. Further criticisms of self-medication hypothesis include the opinion that substance use is rather triggered by withdrawal and craving (Dackis and Gold, 1984) and not by elaborated decisions regarding specific psychopharmacological effects of a certain chemical. Others (Goldsmith, 1993) missed the integration of neurobiological findings, such as the mood regulatory and rewarding effects of psychoactive substances or the 'reward deficiency syndrome' as described by Kenneth Blum and colleagues (1996), which can be potential triggers for recurrent substance use.

4.2. Traumatic life events

4.2.1. Traumatic life events and the onset of substance use

Traumatic life experiences and especially early trauma exposure – such as physical, sexual abuse or neglect– increase the risks of psychiatric disorders in adulthood, including SUD (Khoury et al., 2010). Trauma-related emotional reactivity may further increase the impact of these life events on both post-traumatic stress symptom- and SUD severity (Badour and Feldner, 2013). Therefore, individual differences in emotional reactivity and regulation may highly affect the outcome of such traumatic experiences. Certain psychiatric disorders – such as Borderline Personality Disorder (BPD) or anxiety disorders – also characterized by elevated reactivity to stress and trauma-related cues, as one of the core features of these disorders is heightened emotional reactivity (Sauer et al., 2014). In case of alcohol dependence, reactivity to both stressful life events and alcohol-related cues (e.g. a picture of preferred alcoholic beverage) may lead to enhanced craving and distress (Coffey et al., 2010), which are associated with more frequent substance use. To the best of our knowledge, impact of traumatic or stressful life events on NPS use in relation to emotional reactivity to these events has not yet been studied.

As we have seen in Khantzian's theory, substance use can function as an emotion regulation strategy, however, from another perspective, emotional dysregulation can also occur as a consequence of addictive behaviour. Especially chronic substance abuse might lead to structural and functional changes (e.g. increased CRF response in the central nucleus of the amygdala) that affect the neuronal basis of emotion regulation (Koob and Le Moal, 1997). The impact of

psychoactive substance consumption on impaired emotion regulation may be manifested in the form of psychiatric disorders such as anxiety or mood disorders (McGue and Iacono, 2008), or emotional hyper-reactivity to stressful life events as mentioned above. Both the perception and appraisal of stressful or traumatic life events relies on several aspects, like personality traits, availability of internal resources, current and prior emotional state and specific brain regions such as the amygdala, hippocampus or the insula (Sinha, 2008).

The effectivity of coping with stressful life events or trauma also show high individual variability. As a possible positive outcome, overcoming stressful or emotionally challenging life situations may result in Post-Tramatic Growth (PTG). PTG usually includes the ability to set new life priorities, a sense of enhanced personal strength, identifying novel possibilities in life or even a positive spiritual change (Tedeschi and Calhoun, 1996). PTG was also found to be a relevant protective factor regarding lower frequencies of alcohol use, binge drinking and cannabis consumption (Arpawong et al., 2015). Recovery from addiction can also result in PTG, increasing self-efficacy, the level of family intimacy, closeness with others, compassion and spirituality, self-knowledge and decreasing naivety (McMillen et al., 2001).

On the other hand, failure to successfully overcome such traumatic experiences may lead to low self-esteem or even Post-Traumatic Stress Disorder (PTSD), which is highly associated with SUD (e.g. Reed et al., 2007). Substance abuse in these cases can be interpreted as a maladaptive coping effort. Rates of PTSD among SUD patients are reported to vary between 14% and 60% (Najavits et al., 1997; Brady et al., 2001; Donovan et al., 2001; Triffleman, 2003).

Gender differences also occur in the longterm effects of a traumatic event. While men are more likely to be exposed to traumatic experiences, women are more frequently suffer from high impact trauma with negative longterm outcomes, such as sexual or physical abuse in childhood (Stewart et al., 2002). Women are also more vulnerable to developing PTSD (e.g. Breslau et al., 1997), followed by such trauma.

4.2.2. Traumatic life events and relapse

Regarding the role of negative life events in relapse, recent loss (Krueger, 1981), intimate partner violence (El-Bassel et al., 2005), childhood sexual abuse (Schiff et al., 2010) and family-related conflicts as major life events (Mutasa, 2001) were found to be significant predictors of drug abuse among SUD patients receiving therapy. The effects of negative life events on various mental disorders had been described by former studies (Faravelli et al., 2007; Low et al., 2012; Wardenaar et al., 2014), whereas common psychopathologies such as anxiety or mood disorders may also affect how substance users can cope with stressful life events (Franken et al., 2001).

Emotional stressors, including interpersonal conflicts, loss of relationships, death of a close family member or a child are powerful predictors of relapse during treatment, mainly by inducing craving (Sinha, 2008). The phenomenon that stressful life events may induce craving and relapse is grievously familiar to addiction specialist, working at the clinical field, as a high number of addicted patients rapidly resume the use of psychoactive substances following their treatment due to such reasons.

4.3. Social environment

4.3.1. Psychosocial factors

Substance use vulnerability is significantly affected by psychosocial factors as well, such as family environment, peer pressure, low socioeconomic status, academic underachievement or disorganized neighbourhood. Parents' and siblings' alcohol, tobacco or drug abuse also predicts the individual's own substance use behavior (Gau et al., 2007). According to Gau and colleagues (2007), those youngsters, who prefer to spend their spare time with substance using peers rather than their family, especially when spare time is spent in unsuitable places, are more likely to develop SUDs. Antisocial peers and delinquent behavior were identified as strongest predictors of substance use by others as well (Nation and Heflinger, 2006), mostly among adolescents and young adults. The impact of psychosocial factors on SUD onset and persistence is further increased when a psychiatric disorder is present. The association between parental, sibling and peer influences, SUD and psychiatric disorders was confirmed in the case of comorbid depression (Martin et al.,

2004), anxiety (Lindhout et al., 2009) and conduct disorder (Webster-Stratton and Hammond, 1999).

A study by Kirisci and colleagues (2009) analyzed the relation between individual susceptibility - often cited as *neurobehavior disinhibition (ND)*, which may result in externalizing behaviors – and social environment (peer deviancy) in males and females as potential risk factors regarding the emergence of SUD between childhood and adolescence. As a result, authors found that the association between ND and illicit drug use is mediated by peer deviancy. Age was also found to play a relevant role, as gender differences in the impact of peer influence was significant only in childhood (girls exhibited lower ND scores than boys, and were less inclined to associate with deviant peers). However, by mid-adolescence, gender differences were reduced, as both boys and girls were effected by peer deviancy at age 16.

4.3.2. Recreational scene

With regard to the use of club drugs, including various NPSs, recreational scene itself has a relevant impact on both the first encounter with these psychoactive substances and on persisting substance use as well. In Norman Zinberg's classic model (1986) of drug use ('drug', 'set' and 'setting'), recreational scene (including clubs, discos or hops) can be interpreted as a significant environmental factor, surrounding the occasion of taking specific psychoactive substances. Therefore, on the basis of Zinberg's model, it can be labeled as the 'setting' of drug use. In Hungary, Demetrovics and colleagues (2008) identified intense psychoactive substance use (NPSs like GHB and herbals as well) among recreational users attending clubs. Authors emphasize the relevance of subcultural characteristics in connection with preferred music types. Events related to electronic music (e.g. drum and bass, breakbeat, techno and especially goa parties) is linked to a more frequent drug use. Regarding demographics, the majority of drug using club-goers were 16-25 years old, socioeconomic status was mostly independent from both the frequency and type of substance use.

Situational and emotional triggers (e.g. unpleasant emotions, a desire for spending pleasant times with others or physical discomfort) was found to be associated with an increased frequency of polydrug use in clubs (Palamar et al., 2008). Club drug users are more likely to consume multiple illicit substances (Fendrich et al., 2003), which may result in adverse drug experiences (Lankenau and Clatts, 2005) and drug overdoses (Kerr et al., 2007), mental health problems (Midanik et al.,

2007) and an increased risk of being exposed to infectious diseases (Peters et al., 1998). In the setting of the recreational scene, club drugs – cocaine, MDMA, ketamine, GHB, rohypnol – are often used to enhance sexual experience (Shacham and Cottler, 2010). The use of these substances is also associated with a higher probability of unsafe sex (e.g. not using condoms). Young adults usually prefer club drugs because they have the ability to increase stamina, enabling club attendees to dance all night, and also provide intoxitating and sometimes hallucinogenic highs, deepening their party experience (Kurtz et al., 2009).

Furthermore, contextual characteristics of the recreational scene often include criminal activities that can partly be explained by the psychopharmacological effects of club drugs, increasing aggressive tendencies, reducing user's inhibitions and impairing his/her judgment (Goldstein, 1985). As a result of bivariate logistic regression models, Kurtz and colleagues (2009) predicted arrest histories among party attendees. Most powerful predictive effects across various types of crimes (e.g. theft, shoplifting, burglary, vandalism, aggravated assault, robbery, homicide, rape, possession/distribution of drugs, etc.) were attributed to male gender, histories of substance abuse treatment, physical abuse, childhood victimization and heavy lifetime use of cocaine and marijuana. Exclusively for violent and property crimes, lifetime abuse of MDMA and prescription sedatives alongside with severe clinical symptoms of traumatic stress and fewer years of education were found to be significant predictors.

5. RISKS OF NPS USE

5.1. Psychiatric symptoms

5.1.1. Cathinones

Under the influence of synthetic cathinones, violent acts and unpredictable behavior are common consequences. Users lose touch with reality, dissociative experiences and drug induced psychotic states occur frequently (James et al., 2011; Andrássy et al., 2013). Psychotic episodes or persistent psychosis may be present independently of either family-or individual history of any psychiatric disorder (Dragogna et al., 2014). Such psychotic states are described to be coloured by both visual and auditory hallucinations with menacing or paranoid contents, visual patterns and distrubances (Bajaj et al., 2010). In some cases, anxiety and repeated bursts of inappropriate laughter were observed (Kyle et al., 2011).

Mephedrone-induced catatonia was also identified in a case without significant medical history (Kolli et al., 2013). Low mood and other symptoms of depression were linked to mephedrone consumption as well (Bajaj et al., 2010). As psychostimulants, synthetic cathinones affect learning and memory processes, although at different levels. For instance, in comparison to methylone, mephedrone more intensely reduces working memory (den Hollander et al., 2013), while MDPV also has the potential to produce memory loss, accompanied by severe anxiety, suicidal ideation and aggression (Ross et al., 2012). Further and mainly user-reported adverse effects of synthetic cathinones include bruxism, headache and chest pain related to panic-like states (Dargan et al., 2010; Van Hout and Bingham, 2012).

5.1.2. GHB

Patients with various psychiatric disorders show an elevated risk of developing comorbid SUD and vice versa. This connection between substance abuse and psychiatric problems was demonstrated in the case of GHB as well (Martinotti et al., 2014). High relapse rates (i.e. 85-89%) regarding GHB-dependent patients (Dijkstra et al., 2013) indicate that GHB has a severe addiction potential. Besides its abuse and dependence potential (Galloway et al., 1997) - as described by DSM-IV but not DSM-5 terminology – GHB may induce confusion, incoherent speech and short-term memory loss; symptoms that make individual psychotherapy hardly feasible, if not

impossible. High-risk behaviors are often connected to GHB intake. Comorbid impulsivity leading to riskful situations such as driving or engaging in sexual activites under the influence of this substance was linked to GHB comsumption in these cases (Kim et al., 2007). Anxiety after reducing use, persisting for over one year, insomnia, depression and irritability are further psychiatric symptoms mostly occurring as a consequence of GHB withdrawal (Stein et al., 2011). At higher doses, GHB use may also induce or increase paranoia with auditory and tactile delusions (Couper and Marinetti, 2002). As comorbid psychiatric disorders, anxiety and depression are most typically linked to GHB use (e.g. Miotto et al., 2001).

5.2. Toxicity

5.2.1. Cathinones

Cardiac, psychiatric, and neurological symptoms are the most commonly reported toxic effects of synthetic cathinones (Prosser and Nelson, 2012). In case of mephedrone, agitation, confusion or psychosis, chest pain, nausea, palpitations, peripheral vasoconstriction and headache (James et al., 2011) were found to be relevant consequences of intoxication, alongside with tachycardia, anxiety, mydriasis, hypertension and tremor. In recent years, a growing body of evidence confirmed mephedrone's ability to induce comatose states or even death (Maskell et al., 2011; Schifano et al., 2012; Adamowicz et al., 2013). Similarly to mephedrone, the overdose of other cathinones may results in comparable adverse states. Linked to MDPV overdose, cerebral edema, cardiorespiratory collapse, myocardial infarction, anoxic brain injury and death were reported (Ross et al., 2012). The number of fatal intoxications due to excessive MDPV consumption – and mostly caused by cardiac arrhythmia - also increased over the past few years (Murray et al., 2012; Wyman et al., 2013).

Some studies documented parkinsonism as well in patients following chronic parental use of methcathinone, as explained by manganese contamination of these homemade products (Iqbal et al., 2012). Renal and hepatitc failure, rhabdomyolysis and hyperthermia are further, frequently occurring (Wood et al., 2011; Borek and Holstege, 2012) adverse consequences of synthetic cathinone use.

5.2.2. GHB

Dose-dependent effects of GHB can mainly be explained by its affinity for two receptors in the brain. At low doses, GHB might bind to the GHB-specific receptor (e.g. Maitre et al., 1990) and by doing so, it inhibits presynaptic dopamine release and evokes stimulant-like effects (Feigenbaum and Howard, 1996). At higher doses, GHB stimulates $GABA_B$ receptor resulting in an increase in dopamine levels and inducing depressant effects (Xie and Smart, 1992). High oral doses of GHB (typically greater than 60mg/kg) can result in coma, which usually last up to 4 hours (Mamelak, 1989).

Clinical toxicological studies often use the Glasgow Coma Scale (GCS) scores in order to indicate overall impairment of neurocognitive states. Glasgow Coma Scale was originally used in the assessment of post-traumatic coma and consciousness, mainly among head trauma patients (Teasdale and Jennett, 1974), however, later on it became widely popular in clinical toxicological settings as well. GHB intoxicated patients frequently score less than eight (out of a maximum of 15 points) on the GCS (e.g. Sporer et al., 2003; Krul and Girbes, 2011). In these cases, clinicians need to protect the patient's airway through endotracheal intubation as well as a longer period of time to recover is expected (Lu and Erickson, 2010), although it has also been demonstrated that patients, even with a score of 3 on GCS usually spontaneously regain consciousness within 5 hours of GHB ingestion (Chin et al., 1998). Another important indicator of clinical toxicology is the Poisoning Severity Score (PSS) (Persson et al., 1998), which grades the severity of acute poisoning due to administration of different chemicals, including psyhchoactive substances. PSS has been reported regarding the overdose of many psychoactive substances, such as ethanol, amphetamines, synthetic cathinones (Helander et al., 2014), cocaine (Bodmer et al., 2014) or synthetic cannabinoids (Hermanns-Clausen et al., 2013), athough not specifically in the case of GHB poisoning.

GHB withdrawal, which – similarly to alcohol – often includes symptoms such as anxiety, tremor, agitation, delirium, seizures or even death (Rosenberg et al., 2003; Choudhuri et al., 2013), has also been associated with Wernicke-Korsakoff syndrome (Friedman et al., 1996), characterized by symptoms like confusion, loss of muscle coordination, abnormal eye movements (e.g. nystagmus), loss of memory, confabulation and hallucinations. In these cases, Korsakoff psychosis

results from permanent damage of specific brain areas associated with memory functions, due to Wernicke encephalopathy.

5.3. Injecting NPS use

Increasing injection rates of mephedrone and other illicit substances were recently reported in several countries, such as Austria, Romania, Slovenia, Greece, and Ireland (e.g. Europol-EMCDDA, 2010; EMCDDA, 2011b; Van Hout and Bingham, 2012). Many studies have already described different risk behaviors, such as felony convictions (Domier et al., 2000), difficulty in controlling violent behavior (Zweben et al., 2004), suicide attempts (Darke and Kaye, 2004; Marshall et al., 2011), sexually transmitted infections (Tyndall et al., 2003; Cheng et al., 2010), social stigma (Semple et al., 2004), higher rates of unemployment (White et al., 2006) and patterns of harmful drug use associated with intravenous stimulant use. Furthermore, the intravenous use of mephedrone – compared, for instance to injecting heroin use – is typically associated with a much higher frequency of daily injecting (DrugScope, 2012), which might lead to the rapid damage of syringes and therefore to muscle and vein injuries as well as a greater risk of infections. As powder mephedrone is highly soluble in water, it can easily be dissolved and then injected intravenously or intramuscularly.

In recent years, the phenomenon of drug change also resulted in more harmful patterns of injecting drug use, as former injectors of heroin or other opioids and various psychostimulants started to inject NPSs (i.e. mephedrone, pentedrone and MDPV) with unknown psychological and physiological effects (e.g. Dickson et al., 2010; DrugScope, 2012; Rácz et al., 2012; Csák et al., 2013). The shifting from opioid to cathinone injecting was most markedly present in Hungary and Romania (EMCDDA, 2014a). Adverse consequences of cathinone injecting include skin erosion, localized infections, blood clots, burning sensation at the injection site and increases in HCV and HIV infection rates (Botescu et al., 2012).

6. AIMS AND SEQUENCE OF STUDIES

The lack of empirically proven data about NPSs explains the primary goal of my reseaches, namely the explorative study of mephedrone and GHB. I aimed to explore the use and effects of these substances, in order to provide useful information for later prevention and intervention programs that might target the prevention of NPS use onset or treating persisting NPS use. Assessing the functionality of NPS use was also part of my first goal.

My second goal was to test the relevance and adaptability of three psychological etiological models (see the Etiology section of my thesis) in explaining either the onset of NPS use or persisting use of these substances.

My thesis consists of six empirical studies:

Study 1: The first study (chapter 7.1.) is analyzing web interest on mephedrone in order to assess the connection between mephedrone's legislative status and the rate of mephedrone-related web searches. This study also aims to explore the association between GHB-related web searches and GHB-intoxication cases. Therefore Google Trends is tested as a potential tool for predicting trends in NPS use and its adverse consequences.

Study 2: The second study (chapter 7.2.) is exploring mephedrone's main subjective and somatic effects in order to identify whether or not mephedrone can be an effective substitute for MDMA and other entactogen stimulants. The second and the third study analyzed the same sample of 145 recreational mephedrone users, recruited by snowball method.

Study 3: As the second study showed (Kapitány-Fövény et al., 2013a), a relatively high rate of mephedrone users inject this NPS, which indicated a potentially more harmful pattern of mephedrone use. The third study (chapter 7.3.) therefore aims to assess the differences between injectors and non-injectors of mephedrone, with special emphasis of the severity of psychiatric symptoms. We also analyze the characteristics of first and current mephedrone use, and as such, we test the adaptability of the etiological model regarding the impact of the social environment on NPS use. Furthermore, alongside with the fourth study, we present mephedrone's substitutional potential as an intravenously administered substance.

Study 4: In the third study, we found a high rate of opioid users among mephedrone injectors (Kapitány-Fövény et al., in press-a) and therefore discussed whether injecting mephedrone use or rather opioid use is associated with an elevated psychiatric symptom profile. In order to answer this question, we assessed NPS use – including cathinones – and psychiatric symptoms among a clinical sample of 198 opioid dependent patients. The fourth study (chapter 7.4.) tested self-medication hypothesis by exploring the psychiatric symptoms and reasons of NPS use. As part of this study, we also examined the role of traumatic life events in NPS use as the third selected etiological model.

Study 5: The fifth study (chapter 7.5.) is exploring GHB's toxicity and its role in drug facilitated sexual assaults and acquisitory crimes. In this study we analyze a sample of 352 GHB-intoxicated patients (and altogether 408 intoxication cases), by assessing their medical reports. The main goal of this study is to test GHB's functionality as a potential date-rape drug and to compare intentional and unintentional cases of GHB intake.

Study 6: Finally, the sixth study (chapter 7.6.) is exploring GHB's sexual effects and behavioral correlates (Kapitány-Fövény et al., in press-b). In the fifth study, we found that GHB facilitated sexual assaults are not as common as media reports might suggest and also that a significant proportion of the intoxicated patients are intentional users of this substance. Therefore, in this final study, we aimed to assess a sample of 60 recreational GHB users and test the assumption that one of GHB's main function lies in its sexual enhancing effects. We also tested the role of the social environment in GHB use, as we did in the third study as well.

7. EMPIRICAL RESEARCH

7.1. Study 1.

7.1.1. Goals of study

The main goal of this study was to explore the utility of Google Trends in predicting mephedrone-related trends and also in testing theoretical assumptions of the literature of mephedrone. More specifically, we aimed to test whether a decreasing interest in formerly banned substances – such as cocaine, heroin or MDMA – and the legislative status of mephedrone predict web interest about this NPS. We also aimed to examine the correlation between GHB-related web searches and the number of GHB-intoxications measured at the same month or one month later.

7.1.2. Methods

7.1.2.1. Measures

Google Trends: web search queries

Google Trends presents percentages of total search queries regarding specific search terms during an adjusted time interval. Therefore it can be used to determine how many searches have been done for the given terms we enter, in comparison to the total number of Google searches done during the same time. Google Trends is a useful tool for indicating the fluctuation in web and social interest regarding the selected search terms.

Mephedrone

In Google Trends we used the search term ‘mefedron’ as Hungarian equivalent of mephedrone. We analyzed web search queries within the time interval between January 2004 (as first available Google Trends date) and May 2015 (as current date of the analysis). The first ‘mefedron’ search query rate higher than 0 was dated on February 2010 (see Figure 1 before). Within the same time interval we registered the rates of ‘heroin’, ‘ecstasy’ and ‘kokain’ (as Hungarian equivalent of cocaine) related web search queries as well.

GHB

In case of GHB, we used ‘GHB’ and ‘Gina drog’ (as Hungarian street name for this substance) as search terms. We analyzed Google Trends data between September 2009 and June 2013, the same period of the assessed GHB-intoxication cases. GHB-intoxication cases were

registered in the Clinical Toxicology Ward of Péterfy Sándor Street Hospital Clinic and Casualty Centre (for details, see chapter 7.5.).

Articles and further web-page entries about mephedrone

Regarding mephedrone-related online news and all web-page entries containing the term 'mefedron', data was collected between the 1st of January 2004 (start of Google Trends) and 24th of May 2015, exclusively among hungarian web-pages, using the search engine of Google. Altogether 391 Google search results were identified throughout the given time interval. These search results contained online articles about mephedrone, ads for buying this substance online, forum registries and documentaries about mephedrone. Search results were collected out by their publication data and registered by month. Irrelevant search results, where mephedrone was not mentioned as well as duplicative results were excluded (N=169) and not registered. The majority of the excluded search results were classified advertisements and duplicative results. Followed by exclusion, 222 search results were registered.

The total number of mephedrone-related web search results per a given month were arranged into 4 groups: 1) mephedrone-related online written articles, including both newspaper articles and scientific materials (N=166), 2) mephedrone-related documentaries (short movies) (N=6), 3) mephedrone-related ads (to buy it online) (N=27) and 4) mephedrone-related forum or blog registries (users sharing their experiences with this substance) (N=23).

Legal status of mephedrone and GHB

A dichotomous variable was created to indicate legal status of mephedrone (0= legal, 1=illegal). In Hungary, mephedrone was banned in January, 2011. In the following period, every month we included in our analysis was registered as mephedrone being illegal at the time.

In case of GHB, legal status of this substance was not used in our analysis as it was banned in 2004, the same year of first available Google Trends data.

7.1.2.2. Statistical analysis

Data were analysed by SPSS 17 (SPSS Inc., Chicago, IL, USA). In case of mephedrone, comparison of web search rates (mephedrone, heroin, cocaine and ecstasy), the number of online articles, documentaries, ads and forum/blog entries about mephedrone in connection with the legal and illegal status of this substance was done by using Mann-Whitney U test and Independent Samples t-test. Normality of mephedrone-, heroin-, cocaine-, and ecstasy-related web searches' distribution was examined with Shapiro-Wilk test ($N<2000$). Web searches rates by specific substances were compared by using ANOVA with Bonferroni post hoc test.

A path analysis was conducted using Mplus 6.0 software (Muthén and Muthén, 1998-2007). In this model we used the rate of web search queries for 'mephedrone' as a dependent variable, with legal status of this substance as explanatory variable and the following variables as potential mediators: web search rates for 'heroin', 'cocaine' and 'ecstasy', the number of mephedrone related online articles, documentaries, ads and forum/blog entries. An MLR estimation (maximum likelihood estimation with robust standard errors) was used in this model. Acceptability of models such our's is based on goodness of fit indices. A model is acceptable if root mean square error of approximation (RMSEA)<0.08, comparative fit index (CFI)>0.95, non-normed fit index or Tucker-Lewis index (TLI)>0.95. However, our model was a saturated one without degrees of freedom, therefore fit indices had no relevance in this case (RMSEA=0.000; CFI=1; TLI=1).

Rates of web search queries regarding the terms "GHB" and "Gina drog" provided by Google Trends were correlated with the numbers of GHB intoxication cases during the same time period using Spearman's rank correlation. Correlations were also analyzed with a one-month shift regarding intoxication cases in order to explore whether or not web search queries show higher correlation with intoxications occuring later than the same month.

7.1.3. Results

Pre-and post legislative status of mephedrone

We found significant difference in mephedrone's, cocaine's and ecstasy's web search rates when we compared these in terms of pre-and post-legislative status of mephedrone. Web search rates of 'heroin' did not differ between these two stages of time (Table 4).

With regard to mephedrone related web entries, significant difference occured only in the number of online published articles before and after the legislation of mephedrone. After mephedrone was banned, the number of articles dealing with this substance significantly increased.

Table 4. Web search rates and web entries in connection to the pre-and post-legislative status of mephedrone

	Pre-legislation N=84 months	**Post-legislation** N=53 months	t-test / Mann Whitney U test	Effect size r
Web search rates *Mean (SD)*				
Mephedrone	5.5 (17.8)	5.4 (6.3)	U= 849.5***	r=0.00
Heroin	25.5 (23.7)	27.6 (7.6)	U=2129.5	r=0.05
Cocaine	32.2 (29)	50.7 (11.4)	U=1446.5**	r=0.39
Ecstasy	22 (29.2)	36.6 (8.8)	U=1564.5**	r=0.32
Mephedrone related web entries *Mean (SD)*				
Online articles	0.9 (2.2)	1.7 (2.1)	t=-2.191*	r=0.18
Documentaries	0.04 (0.3)	0.06 (0.3)	t=-0.373	r=0.03
Ads	0.1 (0.6)	0.3 (0.7)	t= -1.559	r=0.15
Forum or blog entries	0.2 (0.5)	0.2 (0.4)	t= 0.106	r=0.00

Notes: *p<0.05; **p<0.01; ***p<0.001. Significant differences (p<0.05) are boldfaced.

Distribution and location of web search queries

Web search rates of mephedrone did not show a normal distribution (p<0.05). A sole peak of 100% of all the web searches for the term 'mephedrone' was observed in September 2010 as an indicator of the most intense web interest about this NPS (SD^2=208.3).

In case of the web search rates of "classic" psychoactive substances - heroin, cocaine and ecstasy – the distributions were not normal either (p<0.05). These search queries showed higher variances (SD^2= 365.6 for heroin, 645.1 for cocaine, and 602.1 for ecstasy). Considering the comparison of web search rates' between mephedrone and these classic chemicals, in case of

mephedrone, we observed lower means in comparison with all of the other substances. Table 5 presents the results of ANOVA analysis.

Table 5. Comparison of web search rates by specific substances

	Mean (SD)	Heroin-related web search rates	Ecstasy-related web search rates	Cocaine-related web search rates
		Mean difference	Mean difference	Mean difference
Mephedrone-related web search rates	5.5 (14.4)	20.8***	22.2***	33.9***

Notes: *p<0.05; **p<0.01; ***p<0.001. ANOVA with Bonferroni post hoc test was used.

This finding indicates that web interest about classic drugs might be more persistent. Furthermore, with regard to geographical distribution of web search queries, location of web searches also showed a higher variability in cases of heroin and cocaine. While web interest was centralized and restricted to Pest county for mephedrone, heroin- and cocaine-related searches were registered from further counties, including Győr-Moson-Sopron, Baranya, Csongrád, Hajdú-Bihar and Fejér.

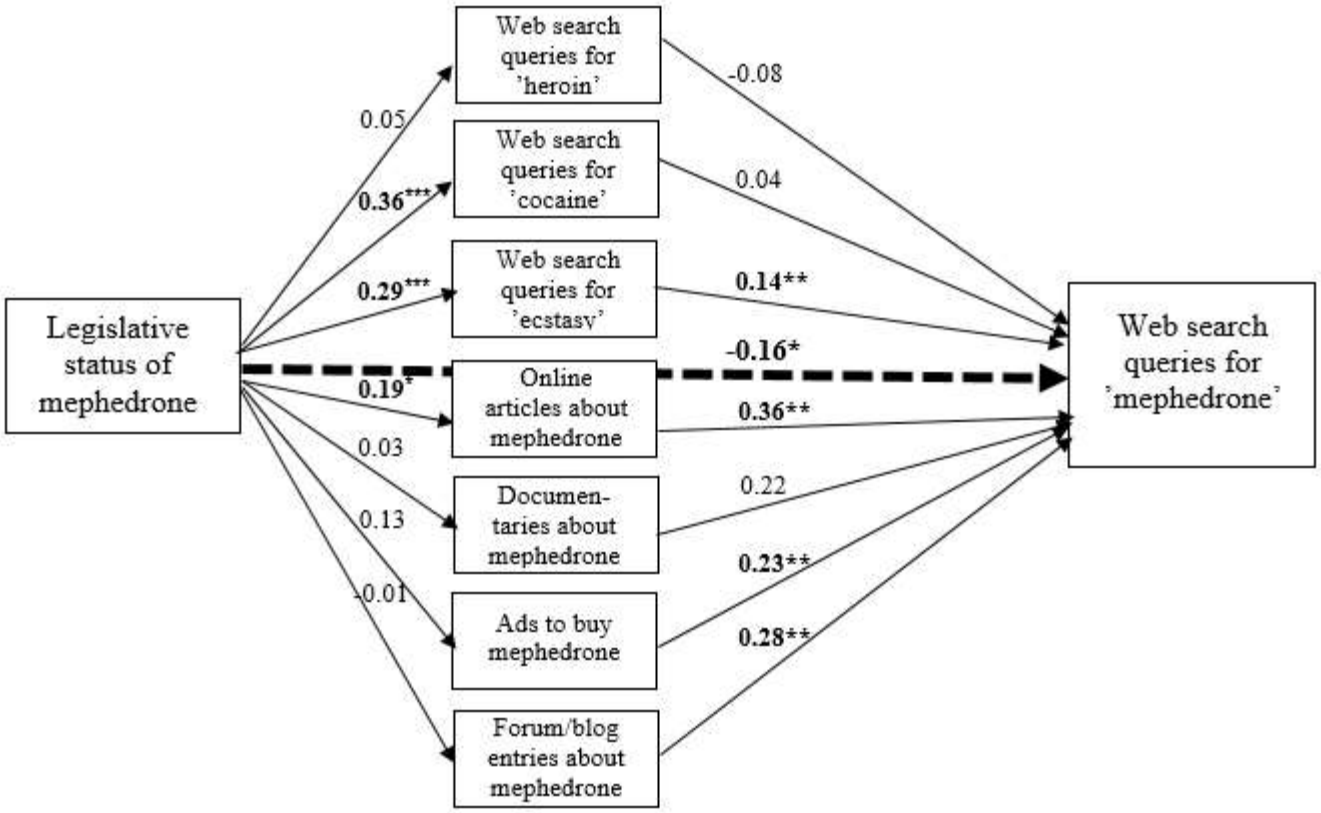
Path analysis: web interest on mephedrone

Illicit status of mephedrone found to be a significant negative predictor of web search query rate regarding the term of 'mephedrone', indicating that web interest was higher when mephedrone was still legal (Figure 3). Legislative status of this substance showed significant and positive connection with web search query rates for 'cocaine' and 'ecstasy' and the number of online articles about mephedrone. The connection between mephedrone-related web search query rate and legislative status of this substance was significantly mediated by ecstasy-related web search query rate, the number of online articles, ads and forum/blog entries about mephedrone.

Mediator variables showed high intercorrelations. Heroin-related web search rate was correlated with both ecstasy ($r=0.52$, $p<0.001$) and cocaine-related ($r=0.78$, $p<0.001$) web search rates, the number of online articles ($r=0.25$, $p<0.001$), ads ($r=0.16$,$p<0.01$) and forum/blog entries (0.17, $p<0.01$) about mephedrone. Ecstasy-related web search rate showed significant correlation

with cocaine-related web search rate (r=0.54, p<0.001), the number of online articles (r=0.24, p<0.001), ads (r=0.19, p<0.01) and forum/blog entries (r=0.22, p<0.01) about mephedrone. Cocaine-related web search rate was in further significant correlation with the number of online articles (r=0.21, p<0.001), documentaries (r=0.10, p<0.01), ads (r=0.15, p<0.01) and forum/blog entries (0.18, p<0.01) about mephedrone. The number of online articles was correlated with the number of documentaries (r=0.38, p<0.01), ads (r=0.38, p<0.01) and forum/blog entries (r=0.59, p<0.001) about mephedrone. The number of documentaries showed significant correlation with the number of ads (r=0.39, p<0.05) about mephedrone, while the number of ads was in significant correlation with the number of forum/blog entries (r=0.34, p<0.05) about this substance.

Figure 3. Web interest on mephedrone as predicted by its legislative status



Notes: *p<0.05; **p<0.01; ***p<0.001. Correlations between mediator variables are not presented in the Figure. Significant correlations are boldfaced.

GHB-related web searches and intoxication cases

The search term ”GHB” assessed in the same month showed a correlation of 0.31 ($p<0.05$) with the number of GHB intoxication cases and a correlation of 0.18 ($p>0.05$) when the date of intoxication cases were shifted with one month. Regarding the search term ”Gina drog”, a correlation of 0.18 ($p>0.05$) was observed in the same month, whereas - when assessed with a one-month shift regarding intoxication cases - a correlation of 0.24 ($p>0.05$) was detected.

7.1.4. Discussion

Our result that the illegal status of mephedrone explained an increase in ecstasy- and cocaine-related web search query rates indicates that web and social interest towards these classic psychostimulant recurred when mephedrone was banned. This finding might confirms the hypothesis that mephedrone’s popularity was highly correlated with its legal status as well as it functioned as a potential substitute for previously banned stimulants. Heroin-related web search rates, however, did not show significant connection with mephedrone’s legislative status. Based on this result we may presume that web interest on heroin as a depressant substance was not relevantly affected by mephedrone’s easy availability.

Illicit status of mephedrone was associated with an increase in the number of online articles published about this substance. This finding might be explained by the fact that shortly after the legislation of mephedrone a high number of informative articles were published in order to report on the legislative changes regarding not only mephedrone but other NPSs as well. A more important result of our path analysis shows that the number of these articles, alongside with the number of advertisements selling mephedrone as well as forum/blog entries about this substance are all positively correlated with mephedrone-related web search rate. The majority of the published articles contained mainly deterrent information about mephedrone (e.g. fatal overdoses or drug-induced psychotic states), whereas online advertisements were promoting mephedrone in order to increase its selling rate. Forum and blog entries contained both positive/confirmative and negative/deterrent information about mephedrone as these entries were mostly users’ reports on their own experiences with mephedrone. Our result therefore indicate that web interest on mephedrone is independent of the content of published information. It might be the frequency of mephedrone being mentioned – in either positive or negative ways - which rather counts in evoking social interest.

Ecstasy-related web search query rate was a significant and positive predictor of the variability of mephedrone-related web search rate. This result might be explained by an increasing web interest regarding club drugs and especially stimulants in general. Furthermore, mephedrone is (or was) the most popular substitute for MDMA (see chapter 7.2.), thus web interest on these substances may be related.

Finally, illicit status of mephedrone was found to be a significant and negative predictor of the variability within mephedrone-related web search rates. Based on this result we may conclude that followed by its legislation, mephedrone's popularity and social interest towards this substance significantly dropped. Users' interest changed and most possibly turned towards even more emerging NPSs, such as MDPV or pentedrone.

In case of GHB, web search queries provided by Google Trends showed moderate but significant correlation with intoxication cases, when the search term of "GHB" was assessed in the same month of the intoxication. Considering this result and the finding of Yin and Ho (2012), the analysis of web search queries regarding certain psychoactive substances might be a useful tool for estimating the rates of intoxication cases due to the overdose of the specific substance. Further research needs to be conducted in order to explore to what extent this marker can be used in the prediction of occurring intoxications.

7.2. Study 2.[1]

7.2.1. Goals of study

The present study aims to reveal the subjective and somatic effects of mephedrone in a systematic way in order to understand how this substance can serve as a potential substitute for entactogens. While doing so, we aim to provide an explanation for mephedrone's functionality and also its outstanding popularity among NPSs.

7.2.2. Methods

7.2.2.1. Sample

Participants were recruited by snowball method. Twelve university students were involved and asked to find mephedrone users among their acquaintances, and have them fill out our questionnaire, while these subjects were also asked to help us in reaching further mephedrone users. The sample consisted of 145 mephedrone users, who had taken mephedrone at least once in their lifetime.

7.2.2.2. Measures

A self complete questionnaire was used that covered the following areas: demographics, substance use experience (regarding past year and past month frequency data separately on both the use of mephedrone and other substances). We generated a list of potential acute subjective and somatic (physical) effects of mephedrone on the basis of former findings regarding mephedrone's main effects (Table 1). Furthermore, we added items of possible stimulant and entactogen drug effects based on the review of the literature. Subjects had to evaluate each acute effect on a 5-point Likert scale according to how often they experienced it as results of their mephedrone use (1 = never, 2 = sometimes, 3 = half of the cases, 4 = most of the time, 5 = nearly always/always). We also asked about post-drug recovery effects of mephedrone in a separate question, however, this data are not presented in the current analysis.

It took approximately 15–25 min to fill out the questionnaire.

Data were analysed by Mplus 6.0 software (Muthén and Muthén, 1998-2007) and SPSS 17 (SPSS Inc., Chicago, IL, USA).

[1] This chapter is based on a published paper, titled ' Substitutional potential of mephedrone: an analysis of the subjective effects' (Kapitány-Fövény et al., 2013a)

7.2.2.3. Statistical analysis

Frequencies of subjective experiences

Mephedrone's most frequently experienced subjective and somatic effects were analyzed by using desciprtive statistics.

Explorative factor analysis

In order to identify factors among the self-reported experience, we performed an exploratory factor analysis with weighted least-squares means and variance adjusted and GEOMIN rotation to evaluate the factor structure of 41 items of subjective experience of mephedrone use.

Acceptability of the factor solution was based on goodness of fit index [root mean square error of approximation (RMSEA) <0.08, close fit (Cfit) (90% CI) >0.50 and comparative fit index (CFI) close to 0.95], the interpretability of the solution and salient factor loadings (>0.40). We examined one-factor, two-factor, threefactor, four-factor, five-factor and six factor solutions.

Fit indices were RMSEA= 0.094, Cfit<.0001 and CFI = 0.614 for one-factor solution; RMSEA= 0.061, Cfit<.008 and CFI = 0.848 for two-factor solution; RMSEA= 0.055, Cfit = 0.132 and CFI = 0.881 for three-factor solution; RMSEA = 0.050, Cfit = .454 and CFI = 0.906 for four-factor solution; RMSEA= 0.047, Cfit = 0.720 and CFI = 0.924 for five factor solution, and finally RMSEA = 0.041, Cfit = 0.936 and CFI = 0.945 for six-factor solution. Because of statistical reasons and the interpretability of the factor structure, the six factor solution was retained (w2 = 728.3 df = 589 p=0.0001).

Latent class analysis: a person-centred approach

We also applied a person-centred approach to examine whether a latent class of users could be identified that shows increases in some subjective effects and not others. The latent profile analysis (Vermunt and Magidson, 2002; Collins and Lanza, 2010) is a latent variable analysis with a categorical latent variable and continuous manifest indicators, such as subjective experience scores of each factors. In the process of determining the number of latent classes, we used the Bayesian information criteria parsimony index (BIC), entropy and the interpretability of clusters. Lower value of BIC and higher value of entropy are usually preferable in model selection. In the final determination of the number of classes, we also used the likelihood-ratio difference test [Lo–Mendell–Rubin adjusted likelihood-ratio test (LRT)] that compares the estimated model with a model having one less class than the estimated model (Muthén and Muthén, 1998–2007). A low p value (p<0.05) indicates that the model with one fewer class is rejected in favour of the estimated

model. We estimated from one-class to three-class solutions. BIC values decreased from one-class to three-class solutions (BIC values were 2094, 2032 and 2007, respectively). The entropies of two-class and three-class were 0.72 and 0.82, respectively. However, two-class solution yielded significant LRT test (LRT value = 93.7, $p<0.04$), and the LRT test for three-class solution was not significant (LRT value = 74.2, $p = 0.379$). In sum, we accepted the twoclass solution.

7.2.3. Results

Sample characteristics

70.8% of the sample were males, the mean age was 24.1 (SD=5.6), 69.4% were living in the capital, Budapest, while 19.4% were resident in other cities and 11.1% in rural areas. 15.2% graduated from a university or college, whereas 58.6% graduated from high school. 54.5% of the sample has either full-time or part-time job. The majority of the sample (87%) reported average or above average living conditions.

Frequencies of experiences

In order to quantify the frequencies of experience, we collapsed the two response categories 'in most cases' and 'almost always/always' and report these proportions. Ten subjective effects were reported in most cases or almost always by more than 50% of participants; pleasant mood, euphoria, ease, feeling oneself close to others, enhanced empathy, suppressed appetite, dry mouth, sharpened perception, insomnia and increased energy.

A question may arise about concurrent substance use, and as a consequence, potential attribution biases regarding the evaluation of subjective effects. To minimise this bias, we asked the participants how often they concurrently use other substances when they are using mephedrone. According to the responses, the majority of the participants never or rarely use other stimulant or entactogenic substances when they are using mephedrone. A total of 83.3% never or just rarely use MDMA at the same time as mephedrone, and the same is true for 77.3% regarding amphetamine, and 92.3% in the case of cocaine. This result indicates that the most frequently mentioned stimulant and entactogenic effects are likely to be caused by mephedrone.

Comparison of mephedrone and MDMA

Besides analysing subjective effects, we also asked participants to directly compare mephedrone with other substances with regards to their subjective effects. MDMA was found to be the most similar substance to mephedrone in its effects, as 48% of the respondents experienced MDMA's effects very similar or nearly the same as of mephedrone. That meant a mean score of 3.3 (1 = not similar at all; 5 = nearly the same), followed by amphetamine (3.1) and cocaine (2.8) (Table 6).

Table 6. Comparison with other substances' subjective effects

	Not similar at all N (%)	Somewhat similar N (%)	Moderately similar N (%)	Very similar N (%)	Nearly the same N (%)	Mean scale score (1-5)
MDMA	8 (6.4)	20 (16)	37 (29.6)	47 (37.6)	13 (10.4)	3.3
Amphetamine	9 (7.3)	24 (19.4)	42 (33.9)	45 (36.3)	4 (3.2)	3.1
Cocaine	23 (20.2)	18 (15.8)	40 (35.1)	29 (25.4)	4 (3.5)	2.8
GHB	45 (50)	23 (25.6)	14 (15.6)	5 (5.6)	3 (3.3)	1.9
Alcohol	65 (46.8)	49 (35.3)	20 (14.4)	4 (2.9)	1 (0.7)	1.8
Heroin or other opiates	64 (75.3)	11 (12.9)	5 (5.9)	3 (3.5)	2 (2.4)	1.5
LSD or magic mushroom	76 (72.4)	22 (21)	6 (5.7)	1 (1)	0 (0)	1.4
Marijuana or hashish	103 (76.9)	22 (16.4)	8 (6)	1 (0.7)	0 (0)	1.3

MDMA, 3,4-methylenedioxy-N-methylamphetamine; GHB, gamma-hydroxybutyrate; LSD, lysergic acid diethylamide.

Factor structure of mephedrone experience

The six factors were positive emotions, sensibility, bodily symptoms, psychological symptoms, stimulant effects and psychedelic effects. The factors and their respective factor loadings are presented in Table 7 as well as the factor correlations. The inspection of correlations between factors revealed a large correlation between the adverse somatic and psychological effects, which demonstrate that those who experience intense somatic effects also experience more intense psychological effects. Sensibility experience also correlates with positive emotions, stimulant effects and the adverse somatic effects.

Table 7. Factor analysis of mephedrone use experience: response frequencies, standardized factor loadings and factor correlations.

	% of most of the times or always	Positive emotions	Sensibility	Adverse somatic effects	Adverse psychological effects	Stimulant effects	Psychedelic effects
		Standardized factor loadings					
Pleasant mood*	80	**0.91**	-0.05	0.17	**-0.42**	0.01	0.01
Euphoria*	68	**0.77**	0.19	-0.06	0.09	-0.03	-0.03
Ease*	68	**0.68**	0.05	-0.06	-0.03	0.24	0.10
Relaxation, calmness	42	**0.62**	0.09	0.08	-0.02	**-0.44**	0.01
Enhanced empathy*	61	0.18	**0.79**	0.11	0.02	0.04	-0.23
Sharpened perception*	52	-0.05	**0.75**	-0.10	-0.07	0.08	0.16
Increased sensibility*	31	0.09	**0.69**	-0.02	0.24	-0.19	0.04
Feeling oneself close to others*	65	0.29	**0.57**	0.00	0.04	0.20	-0.24
Clear consciousness	43	0.09	**0.51**	0.15	-0.35	-0.11	0.18
Painful joints	9	0.01	-0.03	**0.81**	0.07	0.06	-0.09
Tachycardia	32	-0.07	0.11	**0.70**	-0.22	0.25	0.01
Dizziness	6	0.00	-0.10	**0.69**	0.01	-0.17	0.08
Body sweats	40	0.10	-0.13	**0.56**	0.02	0.38	-0.05
Respiratory difficulties	3	0.08	0.06	**0.56**	0.12	-0.17	0.07
Discoloured extremities	6	0.14	-0.20	**0.55**	0.21	-0.07	0.10
Headache	11	-0.01	-0.03	**0.53**	0.05	0.09	0.04
Nausea	4	-0.20	-0.01	**0.48**	0.04	-0.12	0.09
Bruxism	34	-0.04	0.13	**0.48**	-0.07	0.26	-0.09
Dry mouth*	53	0.09	0.26	0.39	-0.04	0.19	-0.02
Contractures, tremors	12	-0.05	0.11	0.35	0.14	0.25	0.16
Dejection, bad mood	21	-0.03	0.31	0.00	**0.82**	-0.13	-0.03
Depressed mood	15	-0.02	0.36	-0.01	**0.78**	-0.02	0.08
Irritability	15	0.07	-0.04	-0.04	**0.64**	0.25	0.36
Fatigue, slothfulness	9	-0.08	-0.04	0.09	**0.64**	-0.43	-0.13
Atony, weakness	4	0.06	0.05	0.25	**0.64**	-0.25	-0.07
Anxiety	15	-0.14	0.35	0.11	**0.58**	0.20	0.16
Concentration difficulties	19	0.06	0.02	0.09	**0.52**	0.31	-0.01
Perplexity	16	0.01	0.03	0.32	**0.48**	0.14	-0.11
Aggression	6	0.02	-0.17	0.02	**0.42**	0.38	**0.42**
Skin irritation	5	-0.03	-0.08	0.20	0.38	0.10	0.20
Stupor, bemusement	33	0.11	-0.13	0.23	0.37	-0.06	0.02
Agitation	40	-0.09	0.04	0.37	0.06	**0.59**	-0.09
Hyperactivity	49	0.12	0.23	0.01	-0.06	**0.56**	0.08
Insomnia, sleeping difficulties*	51	0.01	0.18	0.05	0.24	**0.45**	-0.01
“Toned-up”, increased energy*	50	0.29	0.24	0.01	-0.29	**0.43**	-0.05

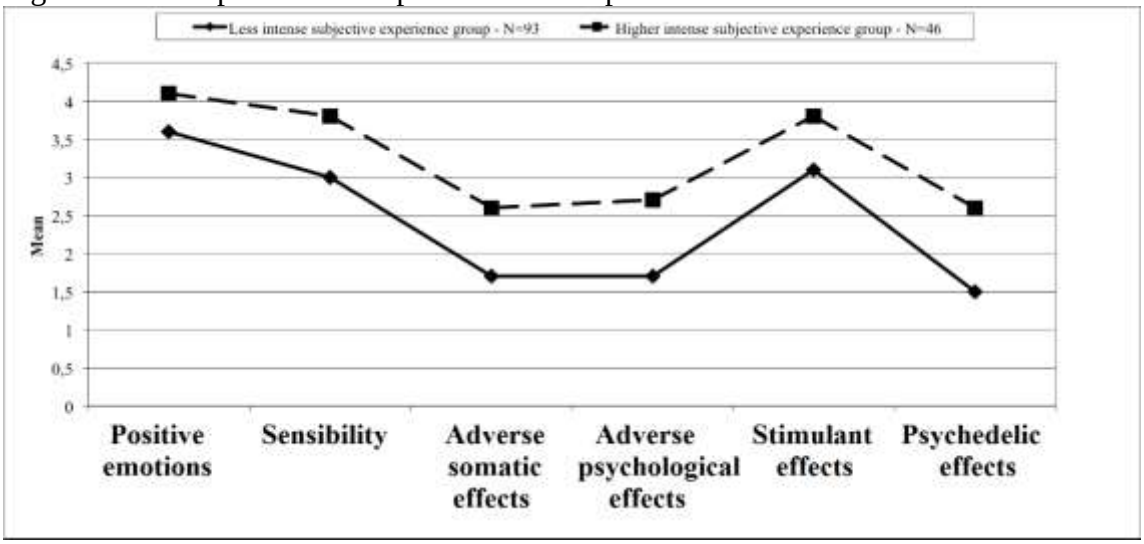
	% of most of the times or always	Positive emotions	Sensibility	Adverse somatic effects	Adverse psychological effects	Stimulant effects	Psychedelic effects
				Standardized factor loadings			
Suppressed appetite*	56	0.18	0.01	0.25	0.13	**0.38**	0.06
Visual hallucinations	12	-0.07	0.09	0.39	0.00	-0.04	**0.71**
Auditory hallucinations	11	0.03	0.07	**0.45**	0.00	-0.01	**0.70**
Loss of memory	7	0.12	-0.01	0.01	0.25	0.10	0.38
Increased sexual desire	33	0.27	0.07	-0.08	0.03	0.13	0.17
Feeling of drunkenness	11	0.02	-0.02	0.10	0.11	-0.24	-0.02
				Correlations between factors			
Sensibility		**0.30**					
Adverse somatic effects		0.15	**0.26**				
Adverse psychological effects		0.01	-0.03	**0.51**			
Stimulant effects		0.16	**0.27**	0.11	0.07		
Psychedelic effects		0.07	0.14	0.16	0.13	0.02	

Note: Frequencies above 50% are marked with an asterisk*. Factor loadings larger than 0.40 are boldfaced. Significant correlations ($p<0.05$) are boldfaced.

Latent classes of mephedrone users

The class profiles are presented in Figure 4. On the basis of their most likely latent class membership, 93 participants belonged to the first class, and 46 persons belonged to the second class. The two classes had closely parallel profiles, indicating that they differed in severity of subjective experience in a way that is consistent across the dimensions. Therefore, almost one third of the participants (33%) reported more intense effects generally.

Figure 4. Latent profiles of mephedrone use experience



A comparison of the latent classes

We compared the two latent classes according to age, gender, presence or absence of intravenous use, the subjective judgement on mephedrone's addictive potential, eight different reasons of use (to reduce stress; for recreation; to exclude everyday problems; to temporarily extinguish everything else; to enhance the sexual experience; to reach altered state of consciousness; to improve self-confidence; and to increase sociability), the average daily dose of mephedrone, and the past year and past month prevalence of mephedrone use in order to examine whether or not these variables can explain the difference between the two classes. Out of these variables, only the subjective judgement on mephedrone's addictive potential and the item referring to the stress reducing effect of mephedrone showed significant difference between the classes. A total of 86.7% of those who belonged to the second class and thus perceived more intense subjective and somatic effects during their mephedrone use considered mephedrone as an addictive substance, whereas in the other group, this proportion was only 68.5%. Similarly, 26.1% of members of the second class reported using mephedrone very often or nearly always in order to reduce stress, while that was only true for 6% of the members of the first class (Table 8).

Table 8. Differences between the two latent classes

		1st class (less intense experience of mephedrone's subjective and somatic effects)	2nd class (more intense experience of mephedrone's subjective and somatic effects	t-test / χ^2	Effect size r
Age *Mean (SD)*		24.4 (5.5)	23.8 (5.9)	t = 0.520	r=0.05
Gender distribution N (%)	Males	69 (74.2)	29 (64.4)	$\chi2$ = 1.400	r=0.1
	Females	24 (25.8)	16 (35.6)		
Intravenous mephedrone use N (%)	Yes	9 (10.1)	6 (13.3)	$\chi2$ = 0.312	r=0.05
	No	84 (89.9)	40 (86.7)		
Is mephedrone addictive? N (%)	Yes	63 (68.5)	40 (86.7)	$\chi2$ = 5.187**	r=0.19
	No	29 (31.5)	6 (13.3)		
Using mephedrone to reduce stress N (%)	Never	62 (66.7)	18 (39.1)	$\chi2$ = 13.717**	r=0.31
	Sometimes to half of the cases	25 (27.4)	16 (34.8)		
	Very often or nearly always	6 (6)	12 (26.1)		
Last year frequency of use N (%)	<2 times	32 (34.4)	11 (23.9)	$\chi2$ = 2.792	r=0.14
	3-9 times	17 (18.3)	13 (28.3)		
	10-39 times	23 (24.7)	10 (21.7)		
	>40 times	21 (22.6)	12 (26.1)		
Last month frequency of use N (%)	None	56 (60.2)	26 (56.5)	$\chi2$ = 0.984	r=0.08
	1-2 times	23 (24.7)	10 (21.7)		
	>3 times	14 (15.1)	10 (21.7)		
Average daily dose of mephedrone (mg) (SD)		1297.8 (903.3)	1143.9 (794.9)	t = 0.836	r=0.09

Notes: *p<0.05; **p<0.01; ***p<0.001.

7.2.4. Discussion

The factor analysis revealed six factors of mephedrone induced subjective effects, which were strongly similar to the symptoms of MDMA as described by several studies (e.g. Downing, 1986; Peroutka et al., 1988; Solowij et al., 1992; Davison and Parrott, 1997; Parrott and Lasky, 1998; Vollenweider et al., 1998). The most frequently reported effects are typical psychostimulant and entactogen symptoms as well as some adverse bodily experiences that indicate that mephedrone, similar to MDMA, is primarily popular for its psychostimulant and entactogen effects. Nine of the ten most frequently experienced symptoms belong to the factors of positive emotions, sensibility and stimulant effects. That means that, although the other three dimensions (adverse somatic effects, adverse psychological effects and psychedelic effects) also colour the experience of mephedrone use, the symptoms that belong to these factors are much less frequently experienced than the former ones.

It also has to be emphasised that among the ten most frequently mentioned effects, there are only three slightly negative or adverse symptoms (suppressed appetite, dry mouth and insomnia), which hints that users tend to evaluate their mephedrone use as a valuable and pleasant experience, rather than a harmful or risky behaviour.

Furthermore, when compared with other substances, users find the effect of mephedrone most similar to that of MDMA. All these results explain clearly why mephedrone is able to substitute MDMA; however, one should also keep in mind that not only mephedrone but also the majority of recreational stimulants share broadly similar effect properties. For instance, in recent placebo-controlled laboratory studies, MDMA's acute effects were found to be very similar to the ones of methamphetamine as well (Parrott et al., 2001; Kirkpatrick et al., 2012). Our findings are similar to the preceding studies (Newcombe, 2009; Psychonaut Web Mapping Research Group, 2009; Dargan et al., 2010; Winstock and Marsden, 2010; Brunt et al., 2011; Winstock et al., 2011b; Freeman et al., 2012) that aimed to analyse mephedrone's subjective and somatic effects.

However, some symptoms, which were mentioned frequently in former studies (such as nausea, discoloured extremities, painful joints, tremor or respiratory difficulties), did not occur among the most frequently referred symptoms in our study. These symptoms were also rare in the study of Winstock et al. (2011a). According to Brunt et al. (2011), mephedrone, in contrast to MDMA, induces strong feelings of craving as well. We did not assess craving or high urge to use

this substance directly, however, we found that 74.3% of our sample considered mephedrone as a substance with addictive potential.

Besides the similar subjective effects, relatively cheap price and easy availability of mephedrone most likely contributed to its success to substitute MDMA. The average price of mephedrone in Hungary (3000-3500 HUF~10 EURO/gramme) is similar to the price of amphetamine and MDMA, and much cheaper than the price of cocaine (15000-18000 HUF~50 EURO/gramme) or heroin (8000-10000 HUF~35 EURO/gramme). We found high correlation between the two factors of adverse somatic and psychological effects, demonstrating that those who experience intense bodily symptoms may also experience more intense psychological effects. The factor of sensibility also correlated with positive emotions, stimulant effects and the adverse somatic effects. These findings support the assumption that positive psychological experience can moderate somatic experiences.

The result of the latent class analysis indicates that there are marked differences in the strength of mephedrone-induced psychological and physiological symptoms in the individual level as well, that is some users—compared with others—react stronger or more sensible to mephedrone. Interestingly, however, the patterns of the experience are the same in both groups. We compared the two latent classes according to many aspects of which only the subjective judgement on mephedrone's addictive potential and the stress reducing reason of use showed significant difference. These results suggest that the more participants perceive intense subjective and somatic effects, the more likely they are to perceive mephedrone as addictive and use it to reduce stress. These differences, however, might require deeper analysis within the confines of a possible future research.

Finally, another topic that needs further analysis is definitely the phenomenon of the relatively high injecting rate. Approximately 12% of our sample administrated mephedrone in an intravenous route. This rate is much higher than the rates reported by the UK studies (Newcombe, 2009; Winstock and Marsden, 2010; Winstock et al., 2011a, 2011b; Freeman et al., 2012) with a range from 0 to 1.2%. Furthermore, in the present study, those who inject mephedrone report to use this substance almost exclusively this way. However, this population, when using mephedrone, seems to substitute rather heroin than psychostimulants. This phenomenon, again, can be explained partly by the low availability of heroin (UNODC, 2011) and the attractive price of mephedrone in comparison with heroin, however, the examination of the psychopharmacological processes

requires further analysis in the future (for details, see chapter 7.3.). However, it should be mentioned that relatively high injection rates were also found among regular MDMA users (e.g. Topp et al., 1999; White et al., 2006; Dunn et al., 2010a, 2010b).

One possible limitation of our study is the possibility of a recall bias regarding the evaluation of mephedrone-induced subjective and somatic effects. Those, who used mephedrone 0 or only 1–2 times last year, may face the difficulty to properly recall mephedrone's typical effects and also to differentiate these effects from other substances' effects. However, if we reanalyse the data after the exclusion of these participants, the most frequently mentioned effects remain the same, suggesting that recall bias might not be substantial in this case.

Looking at these results, we can conclude that mephedrone is able to mimic the effects of other popular psychostimulant and entactogen drugs. By having similar subjective effects as MDMA and other entactogens, mephedrone seems to be suitable to act as a potential substitute for these substances, which can be a reasonable explanation for the popularity of mephedrone in recreational environments. However, there are many questions that remain open for future research. Among others, the comparison of mephedrone's acute and post-drug effects, as well as the development of a standard questionnaire to examine mephedrone's subjective effects could be important research goals.

7.3. Study 3.[2]

7.3.1. Goals of study

In the second study (chapter 7.2.) we found a high rate of mephedrone injectors. Using the same dataset, we therefore aimed to reveal potential differences between injectors and non-injectors of this substance, with special emphasis of psychiatric symptoms. We also aimed to explore the characteristics of first and current mephedrone use (including the social context).

7.3.2. Methods

7.3.2.1. Sample

We analyzed the same sample as we did in the second study. For details, see chapter 7.2.2.1., in which I presented the characteristics of this sample.

7.3.2.2. Measures

We used a self-report questionnaire that covered the following areas: sociodemographic data, substance use experience (last year and last month frequencies of both mephedrone and other substances), characteristics of the first mephedrone use (age, typical location, source and social context of first use), patterns of current use, such as purchase and source of drug, social context of current mephedrone use, typical amount of mephedrone consumed as self-reported measure.

Psychiatric symptoms were assessed using the Brief Symptom Inventory (BSI) (Derogatis, 1975; Derogatis, 1993; Urban et al., 2014), a measure that assesses self-reported clinically relevant psychological symptoms. The 53-item questionnaire uses a 5-point Likert scale (from "not at all" to "extremely"). The BSI comprises nine symptom dimensions: Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism. A summary score of General Severity Index (GSI) can be applied to measure the intensity of general distress. Good reliability and validity has been found across various samples (Derogatis, 1975; Derogatis, 1993; Urban et al., 2014) as well as in the present study (Cronbach's alpha scores regarding the 9 scales were: Somatization= 0.83, Obsession-Compulsion= 0.85, Interpersonal Sensitivity= 0.77, Depression= 0.87, Anxiety= 0.81, Hostility= 0.77, Phobic Anxiety= 0.82, Paranoid Ideation= 0.70 and Psychoticism= 0.73).

It took approximately 15-25 minutes to fill out the entire questionnaire.

[2] This chapter is based on a paper accepted for publication, titled 'Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone?' (Kapitány-Fövény et al., in press-a)

7.3.2.3. Statistical analysis

Data was analyzed by SPSS 17. Spearman's rank correlation coefficient was calculated for exploring whether there was a significant correlation between the frequency of current mephedrone use (frequency of past month use, number of occasions mephedrone is used per day and the self-reported typical daily amount consumed) and psychiatric symptoms, assessed by BSI. For this analysis subjects who injected mephedrone were excluded, since intravenous mephedrone use as a potential confounding variable itself showed connection with both elevated BSI scores and higher doses of mephedrone. We used independent sample t-test and Mann-Whitney U-test in cases of lack of normality, chi-square test and two sample z-test of proportions in order to examine potential differences between injectors and non-injectors of mephedrone. For examining the predictors of the frequency of mephedrone use, multinomial regression analysis was used and 3 groups of users were segregated: 1) Occasional users (less than monthly use of mephedrone); 2) Monthly users and 3) Weekly or daily users. Finally, binary logistic regression was applied to predict injection of mephedrone. McFadden's R2, Cox&Snell's R2 and its adjusted form by Nagelkerke were used as goodness-of-fit measures in our regression models.

7.3.3. Results

Characteristics of first and current mephedrone use

The mean age at the time of the first mephedrone use was 22.7 (SD=6). The majority of the sample (89 subjects; 65.4%) first received mephedrone for free. 131 persons (85.8%) received mephedrone from a close friend or from an acquaintance. Internet was the much less frequently mentioned source of mephedrone, with only 8 subjects (5.7%) reporting this source. A vast majority (134 participants; 93.1%) first used mephedrone with several friends or with one friend. The most frequently mentioned locations of first mephedrone use were discos and parties with 48 subjects (33.3%) reporting these locations.

Regarding current mephedrone use, the self-reported mean dose of mephedrone consumed on a typical occasion was 1345.3 mg (SD=1211.7). 108 subjects (74.5%) buy mephedrone in 74.7% of all mephedrone use cases, while 108 (74.5%) subjects get it for free in 48.9% of all these cases. Close friends or acquaintances were still the most commonly reported sources of mephedrone, with 102 (70.3%) and 90 (62.1%) subjects reporting these sources. The majority of 127 subjects (87.6%) reported that they typically use mephedrone with friends or with acquaintances in 83.1% of all their mephedrone use, mostly in discos or parties, which locations were mentioned by 97 subjects (66.9%) as their typical location of mephedrone use. Intranasal use was the most commonly reported route of administration (123 persons, 84.8%), however, intravenous use was also reported by 11% (16 participants). Oral use was mentioned by 48 participants (33.8%). It must be emphasized that among injectors other routes of administration were not common as they reported using mephedrone this way in 79.5% of all cases (Table 9). Mephedrone was obtained by the participants in almost all cases as powder (93.1%).

Table 9. Characteristics of first and current mephedrone use

First mephedrone use		
Mean age of first mephedrone use	22.7 (sd=6)	
Source of mephedrone N (%)		
Got it for free	89 (65.4)	
Bought it	47 (34.6)	
From a close friend	70 (49.6)	
From an acquaintance	51 (36.2)	
From an unknown person	12 (8.5)	
From the internet	8 (5.7)	
Social context N (%)		
With several friends	81 (56.3)	
With one friend	53 (36.8)	
With partner	4 (2.8)	
Alone	4 (2.8)	
With unknown people	2 (1.4)	
Typical location N (%)		
Disco, party	48 (33.3)	
Other recreational scene	33 (22.9)	
At home	28 (19.4)	
House party (hop)	27 (18.8)	
Bar, pub	8 (5.6)	
Current mephedrone use		
Source of mephedrone	Mentioned by N (%)	Percentage of all mephedrone purchase
Buys it	108 (74.5)	74.7
Gets it for free	108 (74.5)	48.9
From a close friend	102 (70.3)	62.4
From an acquaintance	90 (62.1)	49.2
From an unknown person	45 (31)	31.7
From the internet	25 (17.2)	42.1
Social context	Mentioned by N (%)	Percentage of all social context
With friends or acquaintances	127 (87.6)	83.1
With partner	36 (24.8)	43.4
Alone	35 (24.1)	31.6
With unknown people	23 (15.8)	18.7
Typical location	Mentioned by N (%)	Percentage of all typical locations
Disco, party	98 (67.6)	53.2
At home	73 (50.3)	44.2
House party (hop)	72 (49.7)	36.1
Other place	44 (30.3)	34.8
The way of mephedrone intake	Mentioned by N (%)	Percentage of all mephedrone intake
Sniffing	123 (84.8)	88.9
Oral	49 (33.8)	32.6
Intravenous	16 (11)	79.5
Forms of mephedrone	Mentioned by N (%)	Percentage of all mephedrone intake
Powder	135 (93.1)	94.7
Liquid	17 (11.7)	51.1
Capsule	17 (11.7)	10.9
Pill	13 (8.9)	11.3

Frequency of mephedrone use and psychiatric symptoms

137 participants (94.5%) used mephedrone at least once in the last year, while 58 (40%) used mephedrone also in the past month. Close to one fifth of the respondents (22.8%) used mephedrone 40 times or more during the past year. Regarding the past month, 2.7% reported daily use and another 14.5% used the substance weekly or more often. Self-reported mean dose of mephedrone consumed was 1345.3 mg (95% CI 1126.7, 1563.9). Correlations between indicators of mephedrone use pattern and psychiatric symptoms are presented in Table 10. We found significant correlation between frequency of past month mephedrone use and psychiatric symptom severity as measured by GSI as well as the following BSI subscales: Somatization, Depression, Obsession-Compulsion. The typical daily amount of mephedrone (reported average dose: mg/day) showed significant correlation with GSI and all the BSI subscales, indicating that the more mephedrone is consumed a day the higher the BSI scores are (Table 10).

Table 10. Correlations between mephedrone use and BSI scores

Zero order Spearman correlations between indicators of mephedrone use and psychopathological indices measured with BSI		
	Last month frequency of use	Self-reported typical daily amount
Global Severity Index	0.24*	0.41***
Psychoticism	0.10	0.29**
Hostility	0.17	0.43***
Anxiety	0.10	0.38***
Interpersonal sensitivity	0.02	0.31**
Somatization	0.35***	0.41***
Phobic Anxiety	0.03	0.33**
Paranoid Ideation	0.11	0.37***
Depression	0.20*	0.36***
Obsession Compulsion	0.27**	0.33**

Notes: *p<0.05; **p<0.01; ***p<0.001

Regarding the predictors of mephedrone use frequency – the grouping variable of occasional, monthly and weekly users - multinomial regression analysis indicated that when the predictors were age, gender and GSI, only GSI was a significant predictor of being a group member of weekly or daily users in comparison to occasional users with an odds ratio of 2.95. Males, compared to females, showed a 1.14 times higher odds ratio of being a weekly or daily mephedrone user. When monthly users were compared to occasional users, none of the predictors had a significant predictive value. Results of the second multinomial regression analysis - where distinct BSI scales were entered in the model as independent variables - showed that out of all the BSI scales, only Obsession-Compulsion had a significant predictive value on being a monthly user in comparison to being an occasional user. When weekly or daily users were compared to occasional users, the scales of Somatization and Phobic Anxiety had significant predictive values in the model, however Phobic Anxiety had a negative predictive value regarding mephedrone use frequency (Table 11).

Table 11. A multinominal regression analysis to predict frequency of use of mephedrone

	B (SE)	p	Odds Ratio	95% CI
Analysis 1 (R^2=0.119 (Cox & Snell); 0.137 (Nagelkerke); 0.063 (McFadden)				
Monthly users vs. occasional users				
Intercept	-0.90 (1.12)	.422		
Age	-0.024 (0.042)	.566	0.98	0.90 – 1.06
Gender				
Male	0.27 (0.54)	.617	1.31	0.46 – 3.76
Female	Ref.			
Global severity index	0.56 (0.40)	0.162	1.74	0.80 – 3.80
Weekly or daily users vs. occasional users				
Intercept	1.14 (1.41)	.654		
Age	-0.12 (0.06)	.036	0.88	0.79 – 0.99
Gender				
Male	0.13 (0.53)	.803	1.14	0.41 – 5.21
Female	Ref.			
Global severity index	**1.08 (0.38)**	**.005**	**2.95**	**1.40 – 6.24**
Analysis 2 (R2=0.331 (Cox & Snell); 0.389 (Nagelkerke); 0.211 (McFadden)				
Monthly users vs. occasional users				
Intercept	-0.92 (1.39)	.507		
Age	-0.06 (0.05)	.291	0.95	0.85 - 1.05
Gender				
Male	1.136 .618	.066	3.11	0.93 - 10.45
Female	Ref.			
Psychoticism	-1.54 (0.95)	.107	0.22	0.03 - 1.40
Hostility	-0.36 (0.64)	.574	0.70	0.20 - 2.43
Anxiety	0.03 (0.78)	.972	1.03	0.22 - 4.71
Somatization	0.49 (0.59)	.404	1.64	0.51 - 5.23
Phobic Anxiety	-1.43 (0.75)	.057	0.24	0.05 - 1.04
Paranoid Ideation	0.72 (0.69)	.297	2.04	0.53 - 7.84
Depression	0.28 (0.58)	.629	1.32	0.43 - 4.08
Obsession Compulsion	**1.57 (0.68)**	**.021**	**4.79**	**1.27 - 18.05**
Interpersonal Sensitivity	0.14 (0.69)	.835	1.15	0.30 - 4.45
Weekly or daily users vs. occasional users				
Intercept	0.62 (1.82)			
Age	-0.18 (0.08)	.016	0.83	0.72 - 0.97
Gender				
Male	1.09 (0.79)	.169	2.98	0.63 - 14.14
Female	Ref.			
Psychoticism	-0.98 (1.06)	.357	0.38	0.05 -3.02
Hostility	1.19 (0.70)	.088	3.28	0.84 - 12.82
Anxiety	-0.73 (0.81)	.367	0.48	0.10 - 2.35
Somatization	**2.14 (0.69)**	**.002**	**8.52**	**2.18 - 33.23**
Phobic Anxiety	**-3.02 (1.02)**	**.003**	**0.05**	**0.01 - 0.36**
Paranoid Ideation	0.08 (0.82)	.919	1.09	0.22 - 5.40
Depression	1.13 (0.67)	.092	3.10	0.83 - 11.54
Obsession Compulsion	0.73 (0.75)	.331	2.06	0.48 - 8.90
Interpersonal Sensitivity	0.23 (0.84)	.782	1.26	0.24 - 6.54

Notes: Occasional users were defined as less than monthly use. Significant (p<.05) predictors are boldfaced.

Differences between injectors and non-injectors of mephedrone

Injectors of mephedrone were significantly older, used higher doses of mephedrone on a typical occasion, showed higher frequencies of last month mephedrone use and higher rates of subjects who usually take other substances in order to ease potential adverse effects of mephedrone. There was no significant difference in the number of occasions mephedrone is used per day. However, among injectors a higher proportion of participants considered mephedrone as an addictive substance. Regarding proportions of subjects who used other substances in the past month, only the use of heroin or other opiates showed significant difference between the two groups. Among the group of injectors, a higher proportion of participants used heroin or other opiates in the past month. Furthermore, intravenous users of mephedrone showed higher scores on all the BSI scales and the Global Severity Index (Table 12).

Table 12. Comparison of mephedrone injectors and non-injectors

	Injectors (N=16)	Non-injectors (N=129)	t-test /χ^2/ two-proportion z-test	Effect size r
Age Mean (SD)	29.5 (7.78)	23.4 (4.89)	t = -4.26***	0.42
Gender distribution Males N (%)	10 (62.5)	92 (71.9)	$\chi2$ = 1.18	0.09
Patterns of mephedrone use				
Average dosage of mephedrone consumed (mg) Mean (SD)	2086.7 (1778.39)	1237.4 (1075.89)	t = 2.59*	0.33
Number of occasions mephedrone is used per day Mean (SD)	5.5 (5.16)	5.1 (4.48)	t= -0.35	0.05
Did you use mephedrone in the last month? N (%)	11 (68.8)	47 (36.4)	$\chi2$ = 6.19*	0.21
Do you usually take other substances in order to ease adverse effects of mephedrone? N (%)	12 (75)	59 (48)	$\chi2$ = 4.14*	0.17
Proportion of those who consider mephedrone as an addictive substance N (%)	15 (93.8)	89 (71.8)	z = 1.89*	0.16
Last month frequencies of other substance use				
Proportion of those who used marijuana/hashish in the past month N (%)	10 (62.6)	98 (77.2)	z = -1.29	0.11
Proportion of those who used MDMA in the past month N (%)	7 (43.8)	43 (33.6)	z = 0.81	0.07
Proportion of those who used cocaine/crack in the past month N (%)	1 (6.3)	17 (13.6)	z = -0.82	0.07
Proportion of those who used heroin or other opiates in the past month N (%)	6 (37.5)	4 (3.2)	z = 5.04***	0.42
Proportion of those who used LSD/magic mushroom or other hallucinogens in the past month N (%)	1 (6.3)	16 (12.6)	z = -0.73	0.06
BSI scores				
Psychoticism *Mean (SD)*	1.1 (0.87)	0.6 (0.71)	U= 443.5**	0.3
Somatization *Mean (SD)*	1.3 (0.91)	0.6 (0.7)	U= 454**	0.39
Depression *Mean (SD)*	1.9 (1.2)	0.9 (0.9)	U= 497.5**	0.43
Hostility *Mean (SD)*	1.5 (1.1)	0.7 (0.7)	U= 466**	0.39
Phobic Anxiety *Mean (SD)*	1.4 (1.1)	0.7 (0.81)	U= 530**	0.34
Interpersonal Sensitivity *Mean (SD)*	1.2 (1.12)	0.8 (0.87)	U=641.5*	0.19
Obsession-Compulsion *Mean (SD)*	1.7 (0.89)	0.9 (0.87)	U= 444.5**	0.41
Anxiety *Mean (SD)*	1.1 (1.1)	0.8 (0.73)	U= 466**	0.16
Paranoid Ideation *Mean (SD)*	1.4 (0.73)	0.7 (0.69)	U= 345.5***	0.44
Global Severity Index Mean (SD)	67.9 (31.85)	35.6 (32.73)	t=-3.13**	0.45

Notes: *p<0.05; **p<0.01; ***p<0.001

The predictors of injecting mephedrone use were also examined in a binary logistic regression model. Potential predictors were chosen by the significant results of the comparison of injectors and non-injectors: age, gender, GSI and heroin use (Table 13). Out of these independent variables age, GSI and heroin use had significant predictive value on injecting mephedrone use, however, it was heroin use that showed the highest odds ratio of being a mephedrone injector.

Table 13. Binary logistic regression to predict injection of mephedrone

	B (SE)	**p**	**Odds Ratio**	**95% CI**
Intercept	-8.03 - (2.10)			
Age	0.14 - (0.06)	.014	**1.16**	**1.03 - 1.30**
Gender				
Male	-0.01 - (0.96)	.990	0.99	0.15 - 6.49
Female	Ref.			
Global severity index	1.41 - (0.68)	.038	**4.08**	**1.08 - 15.41**
Heroin use	3.24 - (1.04)	.002	**25.42**	**3.31 - 195.35**

Note: N=113. R^2=0.213 (Cox & Snell); 0.474 (Nagelkerke)

7.3.4. Discussion

Our study shows similar frequencies of mephedrone use and similar or slightly higher mean dosages used than what was reported in earlier studies (Dargan et al., 2010; Winstock et al., 2011a, 2011b; Lea et al., 2011). A possible explanation for the latter result is that the proportion of mephedrone-injectors – who use significantly higher dosages of mephedrone than non-injectors – was higher in our study than in the former investigations. These data confirm the general trend regarding the use of psychostimulants as a category of choice. This trend has been increasing for more than 10 years (Schifano et al., 2005; Martinotti et al., 2014).

Results indicate that social environment plays an extremely important role in both the first encounter with mephedrone, and persistent mephedrone use as well. The majority of subjects first received mephedrone for free and from a close friend or acquaintance, who continue to play an important role in current mephedrone use. The typical locations of first and current mephedrone use were discos and parties. This result emphasizes the relevance of harm reduction programs conducted in these nightlife settings with the aim to minimize the possible harms of recreational

stimulant use. Internet as a possible source of mephedrone was mentioned by only a minority of our sample, which does not affirm information on widespread web-based marketing of mephedrone (e.g. EMCDDA, 2012).

To the best of our knowledge this is the first study to compare injecting and non-injecting mephedrone users. We were able to identify a high-risk group of mephedrone-injectors, who use this substance more frequently and in higher doses than non-injectors, as well as they show more psychiatric symptoms. Furthermore, those injecting mephedrone experience this substance to be more addictive and tend to use other substances – mainly benzodiazepines, marijuana and opiates – to ease adverse effects, especially come-down of mephedrone. This maladaptive way of self-medication may increase the risk of polydrug use. This result is in line with the findings of Van Hout and Bingham (2012) showing that intravenously administered mephedrone has severe and hardly tolerable come-down effects. Considering the route of administration, there is evidence that intravenous drug use itself might contribute to mephedrone's abuse liability and increase risk of addiction (Aarde et al., 2013), however, other studies suggest that mephedrone has an addictive potential irrespective of the form of use (Winstock et al., 2011a, 2011b). The high proportion of non-injectors in our study who also considered mephedrone an addictive substance (71.8%) might also indicate that mephedrone truly has an addictive potential.

The result that injectors use significantly higher self-reported doses of mephedrone than non-injectors might be due to the relatively short duration of mephedrone's effects (e.g. Psychonaut Web Mapping Research Group, 2009; Winstock et al., 2011a), which may increase the risk of repeating the injection at higher doses than those observed in case of oral and intranasal administration (e.g. Lea et al., 2011; Winstock et al., 2011a; Winstock et al., 2011b; Van Hout and Bingham, 2012). Concerning frequency of use, the DrugScope survey (2012) shows that intravenous users of mephedrone may inject up to 20 times per day. Results of the present study indicating that a higher proportion of injectors used mephedrone in the past month as well and the greater number of mephedrone use occasions of injectors on a typical day – the latter result however not statistically significant – bolster the assumption that intravenous administration can lead to a more severe and risky mephedrone use.

We also analyzed the correlation between different indicators of mephedrone use – such as last month frequency of mephedrone use and typical daily amount – and psychiatric symptoms.

Based on these findings, it can be suggested that the typical daily dose of mephedrone is the indicator which shows the highest correlation with psychiatric symptom scores, however it should also be noted that these correlations were typically moderate to low in their strength and cannot be directly linked to mephedrone's acute effects. Results of the multinominal regression analysis confirmed the role of psychiatric symptoms in more frequent mephedrone use, as psychiatric symptom severity, obsession-compulsion and somatization were significant predictors of monthly or weekly/daily mephedrone consumption. Our finding that obsession-compulsion showed connection with increased frequency of mephedrone use can be explained by the common neurobiological impairment of OCD and stimulant dependence. In case of both disorders, functional connectivity of right inferior and superior orbitofrontal cortex was found to be abnormally reduced (Meunier et al., 2012). However, phobic anxiety had a negative predictive value regarding mephedrone use frequency. Respondents with higher levels of phobic anxiety showed a decreased odds ratio of being a member of monthly or weekly/daily mephedrone users. One possible explanation for this finding is a psychometric limitation of this study, namely the possible impact of suppressor effect in our multivariate analyses (Tu et al., 2008) due to the relatively large correlations between psychiatric symptoms measured by BSI.

Contrary to the findings of Zweben and colleagues (2004), hostility was more inherent among mephedrone injectors. This result, on the other hand, is in line with another finding of the same authors suggesting that injecting methamphetamine is associated with a higher frequency of difficulty in controlling violent behavior and also with the results of Novak and Kral (2011) indicating that injecting drug users have higher rates of arrests. It should also be noted that Booth and colleagues (2006) suggest that the injecting use of any drug may be associated with more severe psychiatric symptoms. Based on the above considerations we can argue whether specific substances or rather the route of administration is associated with the severity of psychiatric symptoms. In this study we found that the severity of psychiatric symptoms (GSI) was a significant predictor of injecting mephedrone use, with a 4.08 odds ratio of being a mephedrone injector if the GSI score is elevated.

With regard to the higher proportion of opiate users among injectors of mephedrone in our study, it is also questionable whether the use of mephedrone or rather the use of opiates is associated with higher BSI scores. Based on the results of Marsden and colleagues (2000),

however, it is rather the polydrug use and not opiate use itself that is associated with elevated psychiatric symptom scores. Unfortunately, we cannot presume causal relationship between injecting mephedrone use and elevated psychiatric symptom scores based on a cross-sectional design.

Regarding last month use of heroin or other opiates, a high proportion of current opiate users was found among mephedrone injectors. Results of the binary logistic regression indicated that those respondents who used heroin showed approximately 25 times higher odds of injecting mephedrone. This may indicate that mephedrone injecting is most likely a continuous habit of former or current heroin injectors. Although our sample is hardly big enough to draw further conclusion about the phenomenon of drug change and transition to injecting new synthetic substances, these results may still add to the understanding of these issues. The above findings are in line with the presumption that opiate users started to substitute opiates with other available (new synthetic) illicit substances in order to experience the desirable high, when the availability of heroin declined (Dickson et al., 2010; DrugScope, 2012; EMCDDA, 2012; Rácz et al., 2012; Csák et al., 2013). This phenomenon might be a reasonable explanation for increasing injection rates of not only mephedrone, but other illicit substances as well, reported in other countries (e.g. Europol-EMCDDA, 2010; EMCDDA, 2011b; Van Hout and Bingham, 2012). On the other hand, the most likely reason for mephedrone being an effective substitute for opiates, thus even for substances other than entactogenic stimulants, seems to be the fact that mephedrone can produce intense effects and high (Winstock and Mitcheson, 2010; Van Hout and Bingham, 2012). Furthermore, the popularity of new synthetic stimulants among former users of heroin or other opiates can also be explained by rather practical and not psychopharmacological aspects. Temporary absence of legal risks and easy availability are the most frequently mentioned reasons for transitioning to synthetic cathinones (Cottencin et al., 2014). Changes in the cathinone of choice (mephedrone, MDPV or recently pentedrone) are also linked to their availability (Péterfi et al., 2014).

Limitations to this work must also be highlighted. A relatively small sample was considered for the investigation, although, similar studies investigating patterns of mephedrone use in this very difficult to reach population (Matthews and Bruno, 2010) assessed even smaller samples (Lea et al, 2011; Winstock et al., 2011b; Freeman et al., 2012). Higher rates of mephedrone-injectors were found in comparison to other previous studies, however the small number of intravenous

mephedrone users (N=16) has also to be mentioned as a limitation. It must also be pointed out that it is quite challenging to reach such a hidden population of users of new synthetic substances like mephedrone, mainly because the majority of these users does not seek treatment (e.g. The National Treatment Agency for Substance Misuse, 2012). Another limitation lies in the fact that the typical daily dose of mephedrone was assessed by users' self-reports. Nevertheless, assessing blood or urine samples would have been unrealistic and probably not as valid neither in confines of our study design. Due to this limitation, it is also questionable whether or not users really consumed mephedrone or another stimulant drug instead. With regard to the comparison of injectors and non-injectors, the effect sizes ranged between small and medium according to Cohen's rule of thumb (1988). Overall, it can be emphasized that to our knowledge this is the first investigation to compare mephedrone injectors and non-injectors with regard to patterns of use and psychiatric symptoms.

By identifying and assessing a group of mephedrone-injectors and comparing injectors to non-injectors with regard to various mephedrone use patterns, it can be concluded that intravenous mephedrone use is associated with a higher risk of harmful drug use and with increased possibility of mephedrone being considered as an addictive substance. The association between some characteristics of mephedrone use and psychiatric symptoms are also worth keeping in mind scores correlation between mephedrone use characteristics – independently of the way the drug is administered - and psychiatric symptom scores need to be kept in mind when planning efficient intervention programs for the users of not only mephedrone but other stimulants as well.

7.4. Study 4.

7.4.1. Goals of study

In the previous study (7.3.) we found a relatively high rate of injecting mephedrone users, who also frequently showed a history of opioid use. These injectors showed an elevated psychiatric symptom profile in comparison to those who did not inject mephedrone or consumed opioids. Therefore, in the current study we aimed to assess psychiatric symptoms among a clinical sample of opioid-dependent patients in order to compare patients with and without a history of designer drug abuse, in order to examine whether designer drug use or rather opioid consumption shows association with elevated psychiatric symptoms.

Another goal of this study was to explore reasons behind the use of designer drugs and to examine potential predictors of designer drug use, including emotionally overwhelming life events. Finally, we aimed to study the impact of designer drug use on the perceived intensity of negative life events as well as to analyze whether or not this association is mediated by the severity of psychiatric symptoms. By using a cross-sectional design, our research could not aim to assess any causality.

7.4.2. Methods

7.4.2.1. Sample

Our sample consisted of 198 opioid dependent patients, recruited at the drug outpatient center of Nyirő Gyula Hospital National Institute of Psychiatry and Addiction, the biggest drug outpatient center in Budapest, Hungary. All of these patients are treated with opioid substitution therapy, receiving either methadone or Suboxone (buprenorphine and naloxone) as therapeutic alternatives for heroin and other opioids.

Three university students from the Institute of Psychology (Eötvös Loránd University of Sciences) were involved in collecting data. Data was collected by face-to-face sessions with the participants between April and August, 2014. Subjects' answers were registered by the participating psychology students.

7.4.2.2. Measures

A questionnaire was used that covered the following areas: demographics, treatment characteristics, substance use experiences (including past year and past month frequencies of the use of GHB, mephedrone, pentedrone, MDPV, synthetic cannabinoids or other NPSs). Based on the literature, we generated a list of 14 potential reasons why someone may choose to abuse NPSs instead of classical psychoactive substances such as heroin, cocaine, ecstasy or speed. Subjects had to evaluate each reason on a 5-point Likert scale according to how typical was the specific reason regarding their NPS use (from 0=”not typical at all” to 4=”completely typical”).

Emotionally intense life events (such as conflicts with significant others, loss of children, friends or parents, losing one’s job, divorce, etc.) were assessed by the 28-item short version of the Life Events Scale (Paykel, 1991). Respondents were asked to score how intense emotionally was the specific event for them (from 0= “no emotional effect at all” to 5= “severe emotional intensity”).

Patients’ psychiatric symptoms were assessed using the Hungarian version of Brief Symptom Inventory (BSI) (Derogatis, 1975; Urbán et al., 2014). The 53-item BSI uses a 5-point Likert scale (from “not at all” to “extremely”). It comprises nine symptom dimensions: Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism. Good reliability was found in the present study (Cronbach’s alpha scores regarding the 9 scales were: Somatization= 0.87, Obsession-Compulsion= 0.8, Interpersonal Sensitivity= 0.73, Depression= 0.86, Anxiety= 0.85, Hostility= 0.82, Phobic Anxiety= 0.78, Paranoid Ideation= 0.62 and Psychoticism= 0.66).

7.4.2.3. Statistical analysis

Data was analysed by SPSS 17. Spearman’s rank correlation coefficient was used to explore correlation between potential reasons to use a NPS and patients’ age and educational level. Gender differences in the frequency of these reasons being mentioned were measured by Mann Whitney U-test. Spearman’s rank correlation coefficient was also used to assess the correlation between these demographic variables and the emotional intensity of negative life events. Potential gender differences were measured by using Mann Whitney U-test in this case as well. Differences between patients with and without a history of NPS use in demographics, treatment characteristics, life events and psychiatric symptoms were assessed by using chi-square test, Mann Whitney U-test and

Independent samples t-test. Binary logistic regression was applied to predict NPS use. McFadden's R^2, Cox&Snell's R^2 and it's adjusted form by Nagelkerke were used as goodness-of-fit measures in our regression model.

Finally, a path analysis of structural equation modeling (SEM) was conducted using Mplus 6.0 software (Muthén and Muthén, 1998-2007) in order to explore whether or not the predictive value of being a NPS user on the perceived emotional intensity of interpersonal conflicts is mediated by the severity of psychiatric symptoms (GSI). An MLR estimation was used in this model. Acceptability of models such our's is based on goodness of fit indices. A model is acceptable if RMSEA<0.08, CFI>0.95, non-normed fit index or TLI>0.95. However, our model was a saturated one without degrees of freedom, therefore fit indices had no relevance in this case (RMSEA=0.000; CFI=1; TLI=1), similarly to our former analysis regarding mephedrone related web search queries (7.1.2.2.).

7.4.3. Results

Descriptive characteristics

141 patients (70.8%) were males, the mean age was 39.7 (SD=6.8). The majority of the participants, 143 participants (72.6%) reported to live among average or better than average socioeconomic circumstances. 42 patients (21.2%) were currently unemployed, whereas 71 subjects (35.9%) had persistent and declared job. Regarding highest educational qualification, 91 patients (45.9%) finished vocational schools, 28 patients (14.1%) graduated from high school, while 19 patients (9.6%) had a university degree. With regard to their primary medication, 178 patients (89.9%) received methadone, whereas 20 subjects (10.1%) were currently taking Suboxone as substitute medication. 112 patients (56.6%) reported to had at least one family member with severe alcohol problems, 49 patients (24.7%) had at least one family member with other substance use problems (both legal and illegal substances), while 49 subjects (56.6%) reported that at least one psychiatric disorder was present in the family.

Besides heroin and other opioids, cannabis was the most popular drug among these patients, as 109 patients (55.9%) had been smoking cannabis regularly for years. 64 patients (32.3%) have tried any NPSs at least once during their treatment. Cathinones were found to be the most popular NPSs. Out of the 64 patients who abused any NPSs, 30 patients (46.9%) primarily abused

pentedrone, 13 patients (20.3%) MDPV (often cited as “music”) and 12 patients (18.8%) mephedrone. Other substances such as biococaine, GHB or ketamine was chosen by only 1 or 2 patients as their primarily abused NPS. Regarding pentedrone as the most frequently consumed NPS, 36 patients (56.3%) used pentedrone in the last year, whereas 10 patients (15.9%) used it in the last month as well. Daily use of the chosen NPS occurred in the case of only 3 patients (4.7%). 40 patients (62.5%) of this subsample intravenously administered one or more designer drugs.

Reasons of NPS use

Out of the 14 potential reasons of choosing a NPS instead of a more familiar psychoactive substance, the most typical reasons were curiosity, replacing other drugs and easy availability (Table 14.). As most of the participants abused cathinone-derivatives, these results may be interpreted as typical reasons for choosing a cathinone-type stimulant drug. However, relatively high mean scale score was found in case of the reason indicating the patient did not know what he/she used. In these cases, NPSs were presumably consumed by chance. There were no gender differences in how frequently the patients mentioned these reasons ($p>0.05$). Age showed significant and negative correlation (($r(64)= -0.26$, $p<0.05$) with the reason to substitute other substances, indicating that the older the patient was the less frequently he/she mentioned this reason. Educational level showed significant negative correlation (($r(64)= -0.28$, $p<0.05$) with the reason that NPSs are considered to be more natural.

Table 14. Reasons of NPS use

Reasons of choosing designer drugs	Not typical at all N (%)	Rather not typical N (%)	Sometimes typical, sometimes not N (%)	Rather typical N (%)	Completely typical N (%)	Mean scale score (0-4)
Curiosity	14 (21.9)	6 (9.4)	7 (10.9)	13 (20.3)	24 (37.5)	2.4 (SD=1.59)
Replacing other drugs	21 (32.8)	2 (3.1)	7 (10.9)	10 (15.6)	24 (37.5)	2.2 (SD=1.73)
Availability	18 (28.1)	7 (10.9)	8 (12.5)	10 (15.6)	21 (32.8)	2.1 (SD=1.65)
My friends also used it	23 (35.9)	3 (4.7)	8 (12.5)	10 (15.6)	20 (31.3)	2 (SD=1.71)
More intense subjective effects	28 (43.8)	3 (4.7)	6 (9.4)	11 (17.2)	16 (25)	1.8 (SD=1.72)
I did not know what I use	29 (45.3)	4 (6.3)	6 (9.4)	9 (14.1)	16 (25)	1.7 (SD=1.72)
Low price	27 (42.2)	7 (10.9)	8 (12.5)	8 (12.5)	14 (21.9)	1.6 (SD=1.64)
Legality	45 (70.3)	2 (3.1)	3 (4.7)	5 (7.8)	9 (14.1)	0.9 (SD=1.54)
Shorter effect duration	50 (78.1)	5 (7.8)	4 (6.3)	1 (1.6)	4 (6.3)	0.5 (SD=1.11)
It cannot be detected in urine and blood samples	53 (82.8)	3 (4.7)	3 (4.7)	2 (3.1)	3 (4.7)	0.4 (SD=1.05)
Exotic brand name	55 (85.9)	3 (4.7)	2 (3.1)	0 (0)	4 (6.3)	0.4 (SD=1.02)
I thought that it was more safe	54 (84.4)	2 (3.1)	4 (6.3)	2 (3.1)	2 (3.1)	0.4 (SD=0.97)
Attractive packaging	57 (89.1)	1 (1.6)	3 (4.7)	2 (3.1)	1 (1.6)	0.3 (SD=0.82)
I thought it was more natural	57 (89.1)	3 (4.7)	3 (4.7)	1 (1.6)	0 (0)	0.2 (SD=0.59)

Notes: *Valid percentages are calculated per rows*

Negative life events

Based on the results of the full sample, life events that provoked the highest emotional intensity were loss of a child (mean= 4.9, SD= 0.32), death of the partner (mean=4.4, SD=1.21), death of a relative (mean= 4.3, SD=1.25), conflicts with parent(s) (mean= 4.1, SD=1.23), suicide in the proximal social environment (meam= 4.1, SD=1.5), miscarriage (mean= 4, SD= 1.33) and a severe chronic illness of a relative (mean= 4, SD= 1.29). Most frequently occurring adverse life event was the significant change in the patients' living standards, with 140 patients (70.7%) experiencing this life situation.

With regard to the correlation between the perceived emotional intensity of negative life events and certain demographic variables, age showed significant correlation with emotional intensity of suffering physical abuse from a close relative ((r(26)=0.44, $p<0.05$), whereas educational level did not show significant correlation with the perceived emotional intensity of any life events. However, gender was found to play a relevant role, as significant differences occurred between males and females with regard to the following life events: conflicts with the partner, raising child(ren) alone, pregnancy, own severe illness, the partner's job loss, suffering any violent crime, new member in the household and public proceedings (Table 15). Females showed more intense emotional reactivity to all of these burdensome life situations.

Table 15. Perceived emotional intensity of negative life events

Negative life events	Severity of perceived emotional intensity							Gender differences			
	None N (%)	Minor N (%)	Mild N (%)	Mode-rate N (%)	Severe N (%)	Very severe N (%)	Mean scale score (0-5)	Males N=141 Mean (SD)	Fe-males N=57 Mean (SD)	Mann Whitney U-test	Effect size r
Loss of a child	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	10 (90)	4.9 (SD=0.32)	4.8 (0.41)	5 (0)	U=10	r=0.32
Death of the partner	1 (3.4)	0 (0)	1 (3.4)	4 (13.8)	2 (6.9)	21 (72.4)	4.4 (SD=1.21)	4 (1.58)	4.7 (0.70)	U=80.5	r=0.27
Death of a close relative	5 (4.6)	0 (0)	3 (2.8)	13 (11.9)	13 (11.9)	75 (68.8)	4.3 (SD=1.25)	4.3 (1.24)	4.4 (1.28)	U=1072	r=0.04
Suicide in the proximal social environment	3 (4.9)	2 (3.3)	3 (4.9)	9 (14.8)	5 (8.2)	39 (63.9)	4.1 (SD=1.45)	4 (1.54)	4.4 (1.12)	U=301	r=0.15
Conflicts with parent(s)	1 (1.5)	1 (1.5)	7 (10.3)	10 (14.7)	10 (14.7)	39 (57.4)	4.1 (SD=1.23)	3.9 (1.26)	4.4 (1.14)	U=398	r=0.20
Miscarriage	1 (3)	1 (3)	2 (6.1)	6 (18.2)	5 (15.2)	18 (54.5)	4 (SD=1.33)	4.1 (1.21)	4 (1.51)	U=129.5	r=0.04
Severe or chronic illness of a relative	3 (2.8)	3 (2.8)	6 (5.6)	20 (18.7)	19 (17.8)	56 (52.3)	4 (SD=1.29)	3.9 (1.29)	4.2 (1.29)	U=1085.5	r=0.12
Suffering physical abuse from a close relative	1 (3.8)	3 (11.5)	1 (3.8)	2 (7.7)	5 (19.2)	14 (53.8)	3.9 (SD=1.58)	3.2 (1.95)	4.5 (0.86)	U=52.5	r=0.39
Relevant change in living standard	5 (3.6)	3 (2.1)	14 (10)	32 (22.9)	21 (15)	65 (46.4)	3.8 (SD=1.36)	3.7 (1.29)	4.1 (1.49)	U=1697.5	r=0.15
Death of a close friend	3 (2.5)	4 (3.4)	9 (7.6)	27 (22.9)	26 (22)	49 (41.5)	3.8 (SD=1.28)	3.7 (1.33)	4.2 (1.05)	U=1017	r=0.20
Own severe physical illness	11 (13.1)	0 (0)	7 (8.3)	13 (15.5)	12 (14.3)	41 (48.8)	3.6 (SD=1.73)	3.4 (1.80)	4.2 (1.38)	U=506.5*	r=0.24
Conflicts with partner	4 (3.4)	4 (3.4)	15 (12.8)	28 (23.9)	23 (19.7)	43 (36.8)	3.6 (SD=1.36)	3.4 (1.39)	4.1 (1.19)	U=1127*	r=0.26
Suffering any violent crime	8 (13.8)	4 (6.9)	3 (5.2)	6 (10.3)	9 (15.5)	28 (48.3)	3.5 (SD=1.86)	3 (2.02)	4.5 (0.84)	U=216**	r=0.44
Divorce from partner (marriage)	15 (12.2)	7 (5.7)	8 (6.5)	29 (23.6)	12 (9.8)	52 (42.3)	3.4 (SD=1.75)	3.3 (1.77)	3.6 (1.69)	U=1433.5	r=0.09
Abortion	11 (17.2)	2 (3.1)	5 (7.8)	11 (17.2)	11 (17.2)	24 (37.5)	3.3 (SD=1.85)	2.9 (1.94)	3.8 (1.62)	U=366	r=0.24
Break-up with partner	20 (16.5)	8 (6.6)	9 (7.4)	35 (28.9)	14 (11.6)	35 (28.9)	2.9 (SD=1.77)	2.9 (1.73)	3.3 (1.87)	U=1172.5	r=0.11
Public proceedings	25 (20)	9 (7.2)	20 (16)	23 (18.4)	15 (12)	33 (26.4)	2.7 (SD=1.84)	2.3 (1.84)	3.8 (1.39)	U=857***	r=0.42
Job loss	25 (20.2)	14 (11.3)	15 (12.1)	26 (21)	19 (15.3)	25 (20.2)	2.6 (SD=1.79)	2.5 (1.76)	2.9 (1.85)	U=1371.5	r=0.11
Child(ren) moved out	6 (27.3)	3 (13.6)	2 (9.1)	2 (9.1)	1 (4.5)	8 (36.4)	2.6 (SD=2.15)	3.3 (1.95)	2 (2.22)	U=37.5	r=0.29
Workplace conflicts	7 (15.2)	6 (13)	8 (17.4)	10 (21.7)	6 (13)	9 (19.6)	2.6 (SD=1.7)	2.4 (1.62)	3.2 (1.81)	U=160.5	r=0.23
Retiral	9 (39.1)	0 (0)	2 (8.7)	3 (13)	1 (4.3)	8 (34.8)	2.5 (SD=2.23)	1.9 (2.16)	3.9 (1.86)	U=29	r=0.44
Partner's job loss	17 (32.1)	5 (9.4)	8 (15.1)	10 (18.9)	5 (9.4)	8 (15.1)	2.1 (SD=1.83)	1.4 (1.56)	3.4 (1.65)	U=128***	r=0.47
Change of residence	56 (44.1)	5 (3.9)	16 (12.6)	17 (13.4)	10 (7.9)	23 (18.1)	1.9 (SD=1.98)	1.7 (1.93)	2.4 (2.0)	U=1451	r=0.18
Raising child(ren) alone	11 (50)	1 (4.5)	3 (13.6)	2 (9.1)	0 (0)	5 (22.7)	1.7 (SD=2.07)	0.6 (0.97)	2.7 (2.31)	U=29*	r=0.51
Pregnancy	33 (61.1)	1 (1.9)	4 (7.4)	2 (3.7)	3 (5.6)	11 (20.4)	1.5 (SD=2.1)	1 (1.87)	2.3 (2.23)	U=233*	r=0.30

	Severity of perceived emotional intensity							Gender differences			
	None N (%)	Minor N (%)	Mild N (%)	Mode-rate N (%)	Severe N (%)	Very severe N (%)	Mean scale score (0-5)	Males N=141 Mean (SD)	Fe-males N=57 Mean (SD)	Mann Whitney U-test	Effect size r
Natural disaster	7 (58.3)	0 (0)	1 (8.3)	2 (16.7)	2 (16.7)	0 (0)	1.3 (SD=1.72)	1 (1.58)	2.3 (2.08)	U=8	r=0.33
New member in the family/household	66 (64.1)	3 (2.9)	4 (3.9)	13 (12.6)	8 (7.8)	9 (8.7)	1.2 (SD=1.81)	0.8 (1.49)	2.0 (2.04)	U=850**	r=0.32
Childbirth	36 (83.7)	1 (2.3)	1 (2.3)	0 (0)	1 (2.3)	5 (9.3)	0.6 (SD=1.57)	0.5 (1.33)	1 (2.0)	U=185.5	r=0.15

Notes: *p<0.05; **p<0.01; ***p<0.001. Significant gender differences (p<0.05) are boldfaced.

Differences by NPS use

Patients with and without a history of NPS use were compared in terms of demographics, treatment indicators, life events and psychiatric symptoms (Table 16). Regarding demographics, significant differences occured in age as those patients who used any NPS at least once in their lifetime were younger than those without NPS consumption experiences. Regarding treatment indicators, patients who did not use any NPSs, were in treatment for a longer period of time. Out of emotionally overwhelming life events, we found significant differences in the level of emotional intensity in case of experiencing conflicts with the partner or the parents. For those, who used NPSs, these life events were emotionally more overwhelming. Finally, regarding psychiatric symptoms, with the exception of Somatization and Hostility, NPS users showed higher scores on each symptom scale. A higher Global Severity Index (GSI) was also found among this subgroup.

Table 16. Differences by NPS use

		NPS users (N=64)	**Non-NPS users** (N=134)	t-test /χ^2/ Mann-Whitney U test	Effect size r
Demographics	Gender Males *N (%)*	46 (71.9)	95 (70.9)	χ^2=0.02	r=0.01
	Age *Mean (SD)*	37.8 (6.2)	40.6 (6.83)	t=2.76**	r=0.21
	Living conditions *Mean (SD)*	3.9 (1.19)	3.9 (1.07)	U= 4167	r=0.00
	Educational level *Mean (SD)*	1.7 (1.75)	2.2 (2.02)	U= 3642	r=0.13
	Currently working *N (%)*	44 (68.8)	95 (70.9)	χ^2= 0.09	r=0.02
Treatment indicators	Dose of opioid subsitution medication (mg) *Mean (SD)*	75.4 (39.6)	68.8 (37.7)	t= -1.14	r=0.09
	Years in treatment *Mean (SD)*	5.5 (5.98)	7.5 (5.51)	t=2.41*	r=0.18
	Receiving methadone *N (%)*	57 (89.1)	121 (90.3)	χ^2=0.07	r=0.02
Life events (LES)	**Conflicts with partner *Mean (SD)***	4 (1.22)	3.4 (1.39)	U=1139.5*	r=0.22
	Conflicts with parent(s) *Mean (SD)*	4.5 (0.85)	3.9 (1.37)	U=406.5*	r=0.25
Psychiatric symptoms (BSI)	**Psychoticism *Mean (SD)***	0.9 (0.83)	0.5 (0.61)	U=2994.5**	r=0.26
	Somatization *Mean (SD)*	1.2 (1.07)	1.1 (0.92)	U=3845.5	r=0.05
	Depression *Mean (SD)*	1.8 (1.16)	1.2 (0.97)	U=2921***	r=0.27
	Hostility *Mean (SD)*	1.1 (1.01)	0.8 (0.88)	U=3439.5	r=0.16
	Phobic Anxiety *Mean (SD)*	1.1 (1.05)	0.6 (0.8)	U=3106**	r=0.26
	Interpersonal Sensitivity *Mean (SD)*	1.3 (1.02)	0.8 (0.79)	U=3112.5**	r=0.26
	Obsession-Compulsion *Mean (SD)*	1.2 (0.93)	0.9 (0.81)	U=3132**	r=0.17
	Anxiety *Mean (SD)*	1.4 (0.96)	0.9 (0.88)	U=2945**	r=0.26
	Paranoid Ideation *Mean (SD)*	1.2 (0.79)	0.8 (0.71)	U=2972**	r=0.26
	Global Severity Index Mean (SD)	1.3 (0.82)	0.9 (0.68)	U=2796**	r=0.26

Notes: *p<0.05; **p<0.01; ***p<0.001. Significant differences (p<0.05) are boldfaced.

Predictors of NPS use

As a next step, we used the indicators where these two subgroups showed significant differences as potential predictors of NPS use in a binary logistic regression model (Table 17). Age, conflicts with partner and conflicts with parents were found to be significant predictors of being a NPS user. Conflicts with partner showed the highest odds ratio (OR=12.79), indicating that those patients who face conflicts with their partner as well as they perceive this life event as an emotionally intense experience, has approximately 13 times the odds to at least try NPSs. Regarding age, our result indicates that being younger is also a risk factor for being a NPS user.

Table 17. Binary logistic regression to predict NPS use

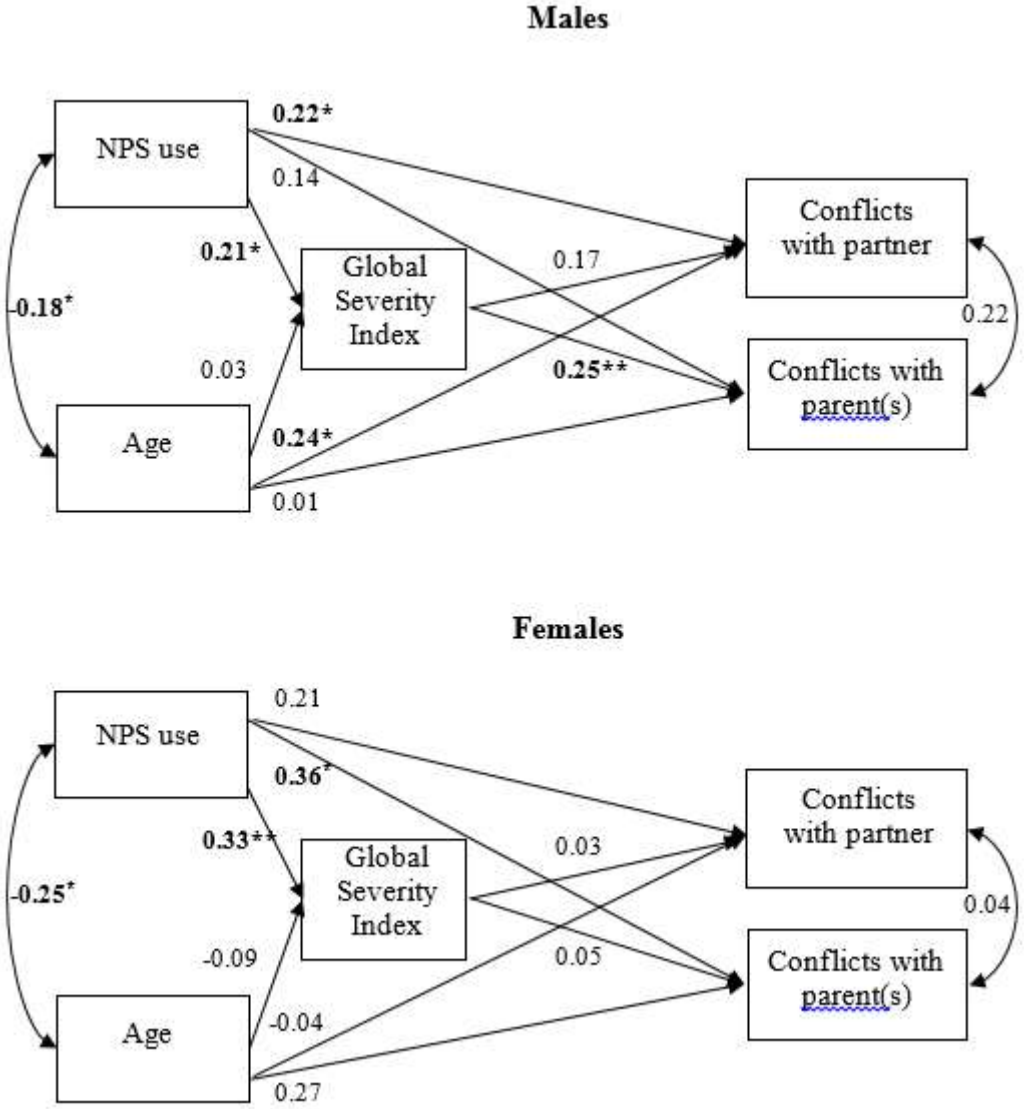
	B (SE)	**p**	**Odds Ratio**	**95% CI**
Intercept	5.68 - (4.37)			
Age	-0.54 - (0.22)	.013	**0.58**	**0.38 - 0.89**
Years in treatment	0.13 - (0.11)	.226	1.14	0.92 - 1.41
Global severity index	-1.48 - (0.91)	.103	0.23	0.04 - 1.35
Conflicts with partner	2.55 – (0.94)	.007	**12.79**	**2.03 – 80.44**
Conflicts with parent(s)	1.48 - (0.65)	.023	**4.39**	**1.23 – 15.71**

Note: N=45. R^2=0.502 (Cox & Snell); 0.673 (Nagelkerke).

Perceived emotional intensity of interpersonal conflicts: a path analysis

As it is based on a cross-sectional design, this research did not assess causality between NPS use, stressful life events and psychiatric symptoms. However, based on former findings (e.g. Franken et al., 2001), it can be hypothesized that the significant association between NPS use and the level of perceived emotional intensity of previously presented interpersonal conflicts is mediated by the severity of psychiatric symptoms. In other words, perceived emotional intensity of interpersonal conflicts can be interpreted as a risk factor for NPS use as well as NPS use itself might have an impact on the perceived emotional level of these life events. Therefore, we finally examined a path analysis model in which NPS use was entered as a predictor variable with age as a covariate, GSI as a mediator variable and conflicts with either the partner or the parent(s) as outcome variables. We analyzed this model separately for males and females (Figure 5).

Figure 5. Psychiatric symptom severity as a mediator between NPS use and the perceived emotional intensity of interpersonal conflicts



Notes: *p<0.05; **p<0.01; ***p<0.001.

In case of males, being a NPS user was associated with higher perceived emotional intensity of having conflicts with the partner. More severe psychiatric symptoms as potential mediators predicted higher perceived emotional intensity regarding the conflicts with the parent(s). Age was also found to be a significant predictor of higher perceived emotional intensity with regard to conflicts with the partner and there was a significant and negative correlation between NPS use and age.

In case of females, being a NPS user predicted higher perceived emotional intensity of having conflicts with the parent(s) and also more severe psychiatric symptoms. Psychiatric symptom severity did not predicted higher emotional intensity regarding interpersonal conflicts. Age and NPS use showed significant and negative correlation.

7.4.4. Discussion

Our results indicate that opioid dependent patients primarily abuse cathinone-derivatives – and mainly pentedrone - but no other NPSs. This result is in line with former findings (Péterfi et al., 2014) that mephedrone, once highly popular, was indeed replaced by other cathinones. We consider the rate of NPS users (32.3%) relevant among this sample, however monthly frequencies of the use of NPSs were found to be quite low. The fact that the majority of our NPS using patients intravenously administered the abused substance confirms the phenomenon that intravenous opioid users transitioned to cathinone-injecting. This phenomenon has been present for years now and still seems to be a currently existing challenge of addiction care.

The assessed reasons of NPS use highlight the leading role of practical or economical aspects as these patients predominantly choose these substances due to their easy availability and capability to substitute other substances, irrespectively of the patient's gender. Psychopharmacological effects of NPSs (such as effect duration or intensity) were less frequently mentioned reasons. This result might contradicts Edward Khantzian's Self-Medication Hypothesis (Khantzian, 1985; 1997), as drug choice of opioid dependent patients is found to be mainly formed by the changes of illicit drug market and not by the psychopharmacological specificities of various chemicals. Therefore, in the absence of heroin, patients of opioid substitution therapy started to inject substances of the easiest availability, in this case, cathinones with psychostimulant properties. Khantzian's SMH remained a relevant theory that generates intense scientific debates, nevertheless, its general applicability has been questioned by others as well (e.g. Lembke, 2012).

In this new era of NPSs, we suggest that SMH cannot be fully applied as an etiological model. The reason that patients did not know what they had been using was also found to be a relevant aspect, indicating that in some cases this choice is rather directed by chance. This random substance use can be considered as a risk factor for severe intoxications or fatal overdoses, due to the unknown compounds of novel street drugs. Demographic variables such as age or educational level showed limited association with the assessed reasons. Patients of higher education were better-informed regarding falsely perceived naturality of designer drugs, whereas older patient showed less intention to substitute their drug of choice.

Younger age was found to be associated with NPS use itself as well as we found significant difference regarding the length of time spent in treatment between patients with and without NPS use histories. This result might be interpreted as a positive treatment outcome, however, it can also be explained by the clinical experience that younger patients with recurrent relapses are more likely to drop out from opioid substitution treatment (Ren et al., 2013; Yang et al., 2013). Our binary logistic regression model suggests that out of the variables that showed significant difference between these two subgroups, perceived emotional intensity of interpersonal conflicts showed the highest odds ratios to be a NPS user. This result emphasizes the relevance of both pair-and family therapy in addiction treatment. Providing services to not just the addicted individual but the whole family is proved to improve treatment effectiveness (Center for Substance Abuse Treatment, 2004).

The severity of psychiatric symptoms was not a significant predictor of NPS use in the binary logistic regression model, however, when we examined the mediating role of GSI between NPS use and interpersonal conflicts in our SEM model, psychiatric symptom severity was found to be a relevant mediator among males, indicating that those male patients who use NPSs not only show more severe psychiatric symptoms, but these psychiatric symptoms can also be linked to a higher sensitivity regarding emotionally overwhelming life events. Furthermore, age as a covariate predicted higher perceived emotional intensity regarding conflicts with the partner, which indicates that aging among male SUD patients may result in enhanced reactivity to relationship conflicts. There were no gender differences in the result that age showed negative correlation with being a NPS user. Younger age therefore can be interpreted as a risk factor for NPS, independently from the user's gender.

The overall elevated psychiatric symptom profile of NPS using patients confirms the assumption of our former study (Kapitány-Fövény et al., in press-a), namely that the use of cathinone-derivatives may be related to highly impaired mental states, and this psychiatric impairment cannot be solely explained by the history of opioid use. Furthermore, the fact that not distinct psychiatric disorders – such as anxiety, mood disorders or OCD – but rather a general psychopathological severity characterizes these cases, may underline the pronounced need of inpatient psychiatric care even more.

Among the limitations of the study, we need to address that NPS use was measured by users' self-reports. We refer to these patients as NPS users, although the majority of them did not use NPSs regularly. Furthermore, as it was already described before, in case of NPSs, users of these substances often do not know what they are really using. Therefore the validity of their answers might be questioned.

7.5. Study 5.

7.5.1. Goals of study

This study aimed to assess the frequency of not only drug facilitated sexual assaults but acquisitory crimes as well as a comparison between intentional and unintentional GHB consumption cases. The study also aims to compare cases with sole GHB consumption with polysubstance use cases in terms of the level of their neurocognitive impairment.

7.5.2. Methods

7.5.2.1. Sample

Data was collected by analysing patients' medical reports of the Clinical Toxicology Ward of Péterfy Sándor Street Hospital Clinic and Casualty Centre, the biggest toxicology centre in Hungary, with around ten thousands patients per year. Medical reports between the 14th of September, 2009 and the 13th of June, 2013 were reviewed. Every patient who admitted GHB use or of whom the clinicians presumed to had used this substance was administered in the database. The names of the patients or any other information which would have made them recognisable – such as their addresses or exact dates of birth - were not entered in our database in order to protect their anonymity. Patients received a patient number instead as well as a case number as a lot of them were treated several times at the same clinical toxicology ward.

7.5.2.2. Measures

Available data from medical reports consisted of epicrisis (the circumstances of the intoxication as the ambulance found the patients or the patient's own statement about the case); heart rate (pulse); serum and urine concentration of GHB, ethanol, amphetamines, cocaine, THC (Δ9-tetrahydrocannabinol), benzodiazepines and opioids; scores of Glasgow Coma Scale and Poisoning Severity Score.

Epicrisis

The epicrisis outlines the patient's chief complaints and responses to administered therapy as well as information about the circumstances of intoxication, such as the location, the time and the social context of the specific case or the presence or absence of blackouts and memory losses. Based on these information further data was collected on potential victimization due to drug

facilitated sexual assault or acquisitory crime as well. Intentionality of GHB use was also registered, based on patients' statements.

Serum and urine concentrations

Serum and urine concentrations (ng/ml) were administered in the database regarding all consumed substances. In case we had data on both serum and urine concentrations of the specific compound, we preferred using urine concentrations during our data analysis procedure.

Glasgow Coma Scale (GCS)

GCS (Teasdale and Jennett, 1974) as a neurological scale assess patients' actual state of consciousness using three distinct indicators: (1) eye opening; (2) verbal response; and (3) motor response. Eye opening is scored on a 4-points scale, where 1=no eye opening, 2= eye opening to pain, 3= eye opening to speech and 4= spontaneous eye opening. Verbal response is scored on a 5-points scale, where 1=no verbal response, 2= incomprehensible sounds, 3= inappropriate words, 4= confused speech and 5= oriented conversation. Motor response is scored on a 6-points scale, where 1= no motor response, 2= stereotyped extension, 3= stereotyped flexion, 4= withdraws (normal flexion), 5= localizes pain, 6= obeys simple commands. The lower the score the greater the presumed neurological impairment is. A maximum of 15 points can be achieved on GCS.

Poisoning Severity Score (PSS)

PSS (Persson et al., 1998) can be used as a classification scheme for cases of acute poisoning, in this case due to psychoactive substance overdose. PSS provides a 5 point severity grading by the observed clinical symptoms and signs, where 0 (none)= no symptoms or signs related to poisoning, 1 (minor)= mild, transient and spontaneously resolving symptoms, 2 (moderate)= pronounced or prolonged symptoms, 3 (severe)= severe or life-threatening symptoms and 4 (fatal)= death.

7.5.2.3. Statistical analysis

Data were analysed by SPSS 17 (SPSS Inc., Chicago, IL, USA) using primarily descriptive statistics. Gender differences regarding poisoning severity were examined by using chi-square test. Chi-square test and independent sample t-test were used in order to examine differences between cases with both GHB and other psychoactive substances detected and cases with only GHB detected, regarding GCS total score, the frequency of experiencing blackouts and the frequency of intentional and unintentional GHB use. Chi-square test and Fisher's exact test were used in the comparison of cases with intentional and unintentional GHB intake, regarding gender distribution and the frequency of sexual assaults and acquisitory crimes.

7.5.3. Results

Sample characteristics

The sample consisted of 352 patients (54% males and 46% females; mean age: 26.9, SD=10.2) who altogether induced 408 treatment cases. The youngest patient was 14 years old, the oldest one was 75 years old. In 182 cases (44.6%) a psychoactive substance was of fact detected, whereas in the other 226 cases (55.4%) either no serum or urine sample was analyzed, or the psychoactive compound has already been metabolised by the time of clinical intervention. Out of the 408 cases, GHB was solely consumed in 113 cases (27.7%), whereas the most frequently co-ingested substance was ethanol, which was detected in 58 cases (14.22%). GHB was of fact detected in 131 cases (34.1%). Out of these cases, ethanol was concomitantly consumed in 15 cases (11.5%). The highest rate of GHB intoxications occured in 2011 with 122 cases (29.9% of all cases). Table 18 shows detailed sample characteristics.

Table 18. Sample characteristics of GHB-intoxicated patients

Demographic and treatment characteristics						
Gender *N (%)*	Male	190 (54)				
	Female	162 (46)				
Mean age *(SD)*	26.9 (10.2)					
Year of treatment *N (% of all cases)*	2009	38 cases (9.3)				
	2010	97 cases (23.8)				
	2011	122 cases (29.9)				
	2012	111 cases (27.2)				
	2013	40 cases (9.8)				
Way of arriving to the toxicology ward *N (% of all cases)*	By own will, alone	8 cases (2)				
	Brought in by ambulance	319 cases (80.4)				
	With police attendance	30 cases (7.6)				
	With relative(s) or acquaintance(s)	40 cases (10.1)				
Substance use characteristics						
Number of treatment occasions in the toxicology ward *N (% of all patients)*	1 treatment occasion	332 patients (94.32%)				
	2 treatment occasions	8 patients (2.27%)				
	3 treatment occasions	5 patients (1.42%)				
	4 treatment occasions	3 patients (0.85%)				
	6 treatment occasions	3 patients (0.85%)				
	15 treatment occasions	1 patient (0.29%)				
GHB detected in serum or urine sample *N (% all cases)*	131 cases (34.1)					
Mean GHB concentration (ng/ml in urine) *(SD)*	6910.76 (10294.02)					
	Ethanol	Benzodiazepine	Amphetamine	Opioid	THC	Cocaine
Other detected psychoactive substances *N (% of all cases)*	58 cases (14.2)	7 cases (1.72)	5 cases (1.23)	2 cases (0.5)	2 cases (0.5)	1 case (0.25)
Mean concentration (blood acohol content or ng/ml in urine) *(SD)*	Blood alcohol content: 1.96 (1.08)	550.78 (457.39)	8000 (0)	1000 (0)	73.58 (0)	5000 (0)

Neurological impairment and poisoning severity

Regarding poisoning severity scores, none of the intoxication cases were lethal, and the majority of both cases with only GHB detected (69.5%) and cases with GHB and other substances detected (85.7%) showed minor poisoning. Severe poisoning occured in 9.6% of all the intoxication cases, whereas 3.8% of the cases showed 'no poisoning'. There was no significant difference in the frequency of severe poisoning between cases of sole GHB detection and cases with GHB and co-ingested substances detected. However, we found gender difference in poisoning severity as among males higher rates of severe poisoning (9.3%) occured. There were no difference between males and females in either GHB's serum or urine concentrations, yet, among females blackouts and memory losses were more frequent (70.4%) and a higher mean of GCS total score was observed.

Gender distribution, GCS total score, the frequency of blackouts and the frequency of intentional and unintentional GHB use were compared between cases with only GHB detected (17 cases) and cases with GHB and other concomitantly consumed substances detected (114 cases) as well (Table 19). Cases with only GHB detected in serum or urine samples showed higher rates of intentional GHB intake (73.1%). However, we did not find significant difference in urine or serum concentrations of GHB, in the frequency of blackouts or memory losses, nor in GCS total score between these two groups.

Table 19. Neurological impairment, poisoning severity and blackouts

Gender differences					
		Males (232 cases)	Females (176 cases)	χ^2/ Fisher's exact test, t-test	Effect size r
Poisoning severity N (%)	None	7 (3.6)	15 (10.1)	χ^2=8.85*	r=0.16
	Minor	136 (70.1)	104 (69.8)		
	Moderate	33 (17)	24 (16.1)		
	Severe	18 (9.3)	6 (4)		
GHB urine concentration (ng/ml) *Mean (SD)*		5502.2 (8335.6)	8055.21 (11794.2)	t=0.65	r=0.12
GHB serum concentration (ng/ml) *Mean (SD)*		1375.19 (2182.9)	993.74 (2066.8)	t= -0.66	r=0.09
GCS total *Mean (SD)*		11.86 (3.6)	12.8 (3.3)	t= -2.59*	r=0.13
Frequency of blackouts or memory losses *N (%)*		128 (57.4)	121 (70.4)	χ^2=10.08**	r=0.20
Differences by detected substances					
		GHB and other psychoactive substances detected (17 cases)	Only GHB detected (114 cases)	χ^2/ Fisher's exact test, t-test	Effect size r
Gender N (%)	Male	9 (52.9)	72 (63.2)	χ^2=0.65	r=0.07
	Female	8 (47.1)	42 (36.8)		
Intentional GHB use *N (%)*		7 (46.7)	79 (73.1)	χ^2=4.39*	r=0.23
GHB urine concentration (ng/ml) *Mean (SD)*		4716.54 (SD=9959.77)	7073.17 (SD=10394.93)	t=0.47	r=0.06
GHB serum concentration (ng/ml) *Mean (SD)*		754.3 (SD=1499.4)	1065.98 (SD=2081.3)	t=0.45	r=0.06
GCS total *Mean (SD)*		11.73 (SD=3.88)	11.73 (SD=3.68)	t= -0.01	r=0.001
Frequency of severe poisoning (PSS) *N (%)*		1 (7.1)	11 (11.6)	p=0.99	-
Frequency of blackouts or memory losses *N (%)*		13 (81.3)	69 (62.7)	χ^2=2.11	r=0.16

Notes: *p<0.05; **p<0.01; ***p<0.001.

Sexual assaults and acquisitory crimes

The frequency of enduring either GHB facilitated sexual assaults or acquisitory crimes under the presumed influence of GHB and other concomitantly consumed psychoactive substances were compared between cases of intentional (111 cases) and unintentional (46 cases) GHB intake (Table 20). We found significant difference in both the frequency of sexual assaults and acquisitory crimes between the two groups as these offences were only observed among unintentional GHB intake cases. Among female patients the frequency of cases of unintentional GHB consumption was higher than among male patients.

Table 20. Intentionality of GHB intake among victims of sexual assaults and acquisitory crimes

		Intentional GHB intake (111 cases)	Unintentional GHB intake (46 cases)	χ^2/ Fisher's exact test	Effect size r
Gender N (%)	Male	84 (75.7)	12 (26.1)	$\chi^2=33.66^{***}$	r=0.46
	Female	27 (24.3)	34 (73.9)		
Frequency of enduring GHB facilitated sexual assaults N (%)		0 (0)	3 (6.5)	p=0.024	-
Frequency of enduring acquisitory crimes N (%)		0 (0)	10 (21.7)	p=0.0001	-

Notes: *p<0.05; **p<0.01; ***p<0.001.

Regarding the results of the full sample (408 cases), GHB facilitated sexual assault occured in 11 cases (2.8%), while acquisitory crimes occured in 38 cases (9.6%).

With regard to the 11 cases (11 different patients) of drug facilitated sexual assaults, 9 patients (81.8%) were females, the youngest patient was a 17 year-old girl, whereas the oldest one was a 53 year-old male (the mean age was 28.9, SD=12.21). GHB was only detected in 2 patients (18.2%) and in 2 other patients (18.2%) only ethanol was detected. However, 6 patients (54.5%) had blakckouts and 3 patients (27.3%) had memory loss. None of them endured any acquisitory crimes and none of them needed intubation as the lowest GCS total score was 12, showed by 2 patients (18.2%).

In the 38 cases (38 different patients) of acquisitory crimes the majority of the victims, altogether 26 cases (68.4%) were males, the youngest patient was a 14 year-old male, whereas the oldest patient was a 75 year-old female (the mean age was 31.5, SD= 14.18). In 25 cases (80.6%) the poisoning severity was minor, moderate poisoning occured in 2 cases (6.5%). None of these patients needed intubation as the lowest GCS total score was 9, represented by 2 patients (5.4%). Blackouts occured in 15 cases (39.5%), memory losses occured in 19 cases (50%). GHB was detected in 9 cases (23.7%), out of which GHB was solely detected in 6 cases (15.8%). Only other psychoactive substances were detected in 5 cases (13.2%) out of which only ethanol was detected in 2 cases (40%), ethanol with other psyhoactive substances (amphetamine, cocaine, THC and benzodiazepine) were detected in 2 cases (40%), whereas in 1 case (20%) only THC was detected.

7.5.4. Discussion

The upward and downward trend of GHB's popularity demonstrated by former studies (e.g. EMCDDA, 2014b) is delineated by our results as well, although we did not assess a representative sample. 2011 was the year with most GHB-related cases (29.9% of all the cases) followed by a decrease in GHB's popularity and resulted in only 40 cases (9.8% of all the cases) in 2013. Some authors describe a rising abuse of GHB in 2014 as well (e.g. Brennan and Van Hout, 2014), indicating that an other upward trend of GHB use may arise. Others highlights that after the ban of GHB, users switched to the use of it's precursor and legal alternative, GBL (γ-butyrolactone), which is now gaining a growing popularity (van Amsterdam et al., 2014).

Demographic characteristics of the 352 patients showed that the sex ratio of GHB-intoxicated patients is rather balanced, except for the cases of unintentional GHB intake, where the rate of female patients was significantly higher than that of males. We found a similar mean age (26.9, SD=10.2) than other studies that assessed samples of GHB users (e.g. Miotto et al., 2001; Degenhardt et al., 2003; Anderson et al., 2006; Krul and Girbes, 2011; Brunt et al., 2013), however our sample consisted of not only voluntary GHB users, but victims of GHB-involved sexual assaults and acquisitory crimes as well. Therefore the result that the majority of the patients were in their twenties can also be explained by the fact that this is also the typical mean age of party-goers who consume psychoactive substances during these recreational events (e.g. Kelly et al., 2006; Parsons et al., 2009), which can be interpret as a risk factor for enduring the above mentioned

GHB-involved offences as well. With regard to concomitant substance use, ethanol was found to be the most frequently consumed psychoactive substance, detected in 13.73% of all the cases and 11.5% of the cases in which GHB was of fact detected. The use of other substances – benzodiazepine, amphetamine, opioid, THC or cocaine – was found to be less inherent. Other researchers (e.g. Couper et al., 2004; Anderson et al., 2006; Liechti et al., 2006) also found ethanol to be the most typical concomitantly ingested substance in case of GHB intoxicated patients, however, according to our results, the concomitant consumption of stimulant drugs was not as frequent as the findings of others would suggest. Our finding that among cases with only GHB detected there were more intentional GHB users suggests that GHB can be the main drug of choice in itself for recreational substance users. On the other hand, approximately half (53.3%) of unintentional GHB users showed combined intoxication with GHB and mainly ethanol, which might support GHB's role as a date-rape drug, added to the drink of unapprehensive victims. Furthermore, due to the interaction of GHB and ethanol in humans, more adverse combined effects can be expected, such as gastrointestinal disturbances, hypotension and decreased oxygen saturation (Thai et al., 2006) which may lead to defenceless states.

To the best of our knowledge, this is the first study that specifically assessed poisoning severity of GHB using the PSS as an indicator. Based on these results, GHB intake either in itself or with a co-ingested substance may usually result in minor poisoning. The frequency of severe poisonings did not differ between cases of GHB detected alone and GHB with co-ingested substances detected, however we found gender differences in poisoning severity. Considering that among males both moderate and severe poisonings occured more often which was found to be unrelated to GHB's serum or urine concentrations, and yet females showed higher rates of blackouts or memory losses, we might state that males seems to be more capable of retaining consciousness under more severe states of poisoning. Fortunately there were no lethal cases in this study, although the highest concentrations of GHB's serum and urine levels were 9561 ng/ml (9.56 mg/l) and 32881 ng/ml (32.88 mg/l). These concentrations are higher than the inclusion cutoffs (5/10 mg/l of GHB's antemortem blood/urine levels) set by Zvosec and colleagues (2011) regarding fatal GHB overdoses. As Brennan and Van Hout (2014) emphasize in their scoping review of GHB's toxicology, levels of lethal dosage can be rather subjective. GHB's neurotoxic potential leading to cognitive impairment is also an understudied area which is to be studied in greater depth, although in recent years studies started to deal with this specific research topic (e.g.

van Amsterdam et al., 2012). Approximately 1/5 (19.8%) of the cases with only GHB detected in serum or urine samples needed endotracheal intubation, which again underlies the potential risk of suffering severe harms due to GHB intoxication, although other studies (Chin et al., 1998; Krul and Girbes, 2011) found even higher rates of GHB-intoxicated patients with a GCS total score less than 8.

The finding that GHB facilitated sexual assaults and acquisitory crimes only occured among cases of unintentional GHB intake suggests that GHB is indeed used as an instrument of criminal offences even after considering the fact that GHB was detected only in 2 cases. However, we should also keep in mind that intentionality of substance use itself can affect observer attributions of a victim of a sexual assault. As Angelone and colleagues (2007) emphasize in their paper, when the substance use – e.g. GHB use - is voluntary, the sexual intercourse is more likely defined as not rape, opposed to unintentional substance intake. One could also argue whether or not cases in which patients establish sexual intercourse under the influence of voluntary GHB use can be considered as sexual abuse, even when the patient would not label these cases as sexual assaults. Another bias regarding this matter would be the rather subjective evaluation of patients' intentionality of substance use as patients of a toxicology ward might tend to deny their illicit substance use and therefore state that the specific substance was unintentionally consumed. The validity of self-reported substance use has been questioned in terms of research findings as well, usually with comparison of the results of blood, urine or hair samples (e.g. Preston et al., 1997; Mordal et al., 2011).

If we presume that all the 408 cases in our database can be linked to either intentional or unintentional GHB intake, the frequency of enduring GHB facilitated sexual assaults is still quite low (2.8% of the full sample), however this result is in line with the findings of former similar studies in which GHB was detected in 1 to 5% of all drug facilitated sexual assaults (ElSohly and Salamone, 1999; Varela et al., 2004; Du Mont et al., 2010). Among those cases of self-reported unintentional GHB intake we found a higher rate (6.5%) of endured GHB facilitated sexual assaults. Among intentional GHB use cases, no sexual assaults occured. Our result that among victims of drug facilitated sexual assaults there were male patients as well cannot be mentioned as an unusual finding, since victims of both childhood and adulthood sexual abuse are often men, although it is the female gender which was found to be a risk factor for the increased likelihood of

sexual victimization (e.g. Xu et al., 2013). The validity of our result might also be impacted by the potential underreporting of sexual offences. Fear of sigmatization, feeling of shame and humiliation, fear of being judged as gay, isolation, negative schemas about the self and denial are the most typical consequences of sexual victimization that also lead to underreporting these assaults in case of both male and female victims (Lisak, 1994; Sable et al., 2006). Yet some authors describe that this kind of underreporting more frequently occurs when the victim is male due to reasons such as the perceptions that men – in noninstitutionalized settings - are rarely sexually victimized or that men are more responsible for their assaults and less traumatized by them (Bullock and Beckson, 2011). The high frequency of blackouts (in 55.6% of the cases where GHB alone or GHB with an other psychoactive substance was detected) indicates that GHB has the potential to provoke irresponsive and defenceless states that on one hand can be a risk factor of being a victim of sexual or acquisitory crimes, but on the other hand often makes these abuse cases unverified.

Based on our finding that in 9.6% of all the cases an acquisitory crime occured alongside with the result that intentional GHB use was not reported in any of these cases, we can conclude that in contrast with media reports, where GHB is typically labeled as a *roofie*, this substance is misused in order to steal the victim's belongins rather than as a date rape drug, even if GHB was only detected in 23.7% of the cases of acquisitory crimes. We also note that the majority (68.4%) of the victims of GHB-involved acquisitory crimes were males. This result again needs to be considered when reporting GHB-related offences, as media news and even scientific papers tend to neglect the fact that among victims of GHB-involved crimes there are men as well.

Both our and former results (Németh et al., 2010) indicate that the use of GHB as a date-rape drug is a factual but not as frequent threat as media report might suggest. It is rather voluntary GHB use that shows linkage with drug-influenced sexual behavior as users intentionally tend to consume GHB in order to enhance their sexual experience (Laborit, 1972; Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008).

One of the main limitation of our study lies in the fact that in the majority of the assessed cases (65.9%) GHB was not detected. As a matter of course it does not mean that in these cases there was no GHB consumption at all. As we have already mentioned, the short half-life of GHB makes it difficult to resolve this ambiguous question. Furthermore, we had no specific data about how much time passed since the psychoactive substance was consumed. However, if we compare

our data with data based on only self-reports of GHB users – questionnaire-based studies or focus-group studies – the fact that we accessed patient's serum or urine concentrations can also be mentioned as one of the strengths of this study. Another limitation which also arives from the methodology of this study, is that we only assessed medical reports instead of directly asked patients about the detailed characteristics of their intoxication. The epicrisis from which we gathered our data therefore can be significantly biased by the subjective judgement of both the ambulance and the physicians.

7.6. Study 6.[3]

7.6.1. Goals of study

As the results of our former study (see chapter 7.5.) indicated that the use of GHB as a date-rape drug might be a factual but not as frequent threat as media report might suggest, we considered voluntary GHB use to show a stronger linkage with drug-influenced sexual behavior, as users rather intentionally tend to consume GHB in order to enhance their sexual experience. Therefore, the aim of this study was to focus on and measure the sexual correlates of such GHB use, the possible impact of this substance on users' sexual experiences and related risky sexual behaviors. We also aimed to confirm sexual enhancing effects of GHB described by former qualitative and observational studies within the confines of a quantitative study. Additionaly, we aimed to examine to what extent GHB is used intentionally with a goal to enhance sexual behavior or as a mean of sexual assults. Our final research goal was to explore potential gender differences in GHB's sexual effects and correlates.

7.6.2. Methods

7.6.2.1. Sample

Participants were recruited in Budapest by snowball method in order to reach as wide and heteregeneous sampe of this hard to reach population as possible. Considering the fact that GHB users often remain a hidden population, treatment seeking patients were not considered. Fourteen university students were asked to find participants, who have used GHB at least once in their lifetime. Participants filled out the questionnaire and then often refered the researchers to other GHB users. Our final sample consisted of 60 GHB users.

7.6.2.2. Measures

A questionnaire was used to assess the following areas: demographics, substance use experience (GHB and other substances), GHB's effects and sexual correlates and the frequency of experienced black-outs as a result of GHB use. A list of potential acute subjective and somatic symptoms of GHB was generated on the basis of former findings (Laborit, 1972; Miotto et al., 2001; Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008; Sumnall et al.,

[3] This chapter is based on a paper accepted for publication, titled 'Enhancing sexual desire and experience: An investigation on the sexual correlates of gamma-hydroxybutyrate (GHB) use' (Kapitány-Fövény et al., in press-b)

2008). Subjects were asked to evaluate each acute symptoms on a 5-point Likert scale according to how often they experienced it as results of their GHB use (1 = never, 2 = sometimes, 3 = half of the cases, 4 = most of the time, 5 = nearly always/always). Participants were also asked to list the three most typical, the three most beloved, and the three most adverse effects of GHB. Separate items on a same 5-point Likert scale covered GHB's specific sexual effects, whereas 8 potential reasons of GHB use – based on users online reports and the findings of former studies (Lee and Levounis, 2008; Sumnall et al., 2008) were also evaluated. Further questions aimed to reveal patterns of subjects' choice of sexual partners with seven response categories (0= never, 1= to a maximum of 10% of all the GHB use cases, 2= 10 to 40% of all the GHB use cases, 3= approximately in 50% of all the GHB use cases, 4= more often than 50% of all the GHB use cases, 5= nearly always when using GHB, 6= always when using GHB).

7.6.2.3. Statistical analysis

Considering the relatively small sample size without sufficient statistical power for multivariate analysis, our results are based on mainly descriptive statistics. Correlations between GHB use frequencies (past month frequency of use, self-reported mean dose of GHB) and various reasons of the use as well as the frequency of experiencing certain sexual effects of GHB were calculated by Spearman's rank correlation coefficient, gender differences in the subjective, somatic and sexual effects of GHB and the reasons of GHB use were calculated by Mann Whitney U test, while Fisher exact test was used to analyze gender differences regarding the choice of sexual partners under the influence of GHB.

7.6.3. Results

Sample characteristics

Two thirds (40 subjects, 66.7%) were male. The mean age was 25.6 years (SD=4.6). 43 respondents (71.7%) were currently single, 17 (28.3%) were in a relationship, but none of the participants were married. 25 subjects (43.1%) did not have a job, 16 (27.6%) worked part time, while 17 (29.3%) had a full-time job. Regarding educational background, the majority, 35 participants (58.3%) graduated from high school, while 12 subjects (20%) graduated from a college or university. Exactly half of the sample (30 participants [50%]) were not studying currently, whereas the other half of the sample took part in either full-time or part-time education. The majority of the sample, 38 participants (63.3%) did not use GHB in the past month, and only 2 participants (3.4%) were regular (daily users). 18 participants (30%) did not consume GHB in the past year, whereas 10 subjects (16.7%) were monthly users of this substance.

First and current GHB use experience

As we have seen it in the case of mephedrone as well (chapter 7.3.), both the first encounter with GHB and persisting consumption usually occur within the social context of peer substance use (mostly with friends). The majority got GHB for free, most frequently from a close friend. Typical locations for first and current GHB use are discos, parties and hops. Regarding current use, the role of unknown individuals and the internet as potential sources of the drug were found to be more relevant than in the case of the first encounter with GHB. The majority of the sample usually consumes GHB in the form of liquid (Table 21). The mean age of the first GHB use experience was 22.1 (SD=4.9).

Table 21. Characteristics of first and current GHB use

First GHB use		
Mean age of first GHB use (SD)		22.1 (sd=4.93)
Source of GHB N (%)		
Got it for free		55 (96.5)
Bought it		2 (3.5)
From a close friend		28 (50)
From an acquaintance		20 (35.7)
From an unknown person		6 (10.7)
From the internet		1 (1.8)
Other source		1 (1.8)
Social context N (%)		
With several friends		39 (66.1)
With one friend		13 (22)
With partner		5 (8.5)
With unknown people		1 (1.7)
Alone		0 (0)
Typical location N (%)		
Disco, party		23 (39.7)
House party (hop)		16 (27.6)
At home		11 (19)
Other recreational location		5 (8.6)
Bar, pub		3 (5.2)
	Current GHB use	
Source of GHB	Mentioned by N (%)	Percentage of all GHB purchase
Gets it for free	55 (91.7)	78.1
Buys it	35 (58.3)	40.1
From a close friend	47 (78.3)	59.3
From an acquaintance	39 (65)	48.2
From an unknown person	24 (40)	17.3
From the internet	12 (20)	27.5
Social context	Mentioned by N (%)	Percentage of all social context
With friends or acquaintances	56 (93.3)	86.2
With partner	18 (30)	40
Alone	15 (25)	17.3
With unknown people	13 (21.7)	7.3
Typical location	Mentioned by N (%)	Percentage of all typical locations
Disco, party	43 (71.7)	51.9
House party (hop)	42 (70)	45.1
At home	24 (40)	38.3
Other recreational scene	20 (33.3)	27.3
Forms of GHB	Mentioned by N (%)	Percentage of all GHB intake
Liquid	51 (85)	94.5
Powder	16 (26.7)	47.2
Pill	10 (16.7)	24
Capsule	9 (15)	9.4

Subjective and somatic effects of GHB

42 participants (70%) has used GHB in the last year, and half of them has used GHB at least once in the last month as well. With regard to other substance use in the last month, 33 subjects (55%) has smoked cannabis at least once, 16 (27.1%) used MDMA, 14 (23.7%) used cocaine, while 2 persons (3.5%) used heroin or other opiates, 2 (3.5%) used LSD or magic mushroom, and only one used any inhalants. The majority (96.7%) drank alcohol at least once in the past month.

The ten most frequently rated subjective and somatic effects of GHB were the following: pleasant mood and euphoria were the most frequently experienced subjective effect mentioned by 35.6% and 35.1% as nearly always or always experienced when using GHB, followed by the feelings of ease, tranquility, feeling of being close to others, feelings of being drunk, and experiencing stupor. On the other hand, however, increased sexual arousal, sharpened perception, and hyperactivity were also among the ten most frequently experiences symptoms. Males experienced euphoria and hyperactivity more frequently than females (Table 22.).

Table 22. Subjective and somatic effects of GHB

Most typical subjective and somatic effects	Never N (%)	Some-times N (%)	Half of the cases N (%)	Most of the cases N (%)	Nearly always/ always N (%)	Gender differences			
						Mean scale score (SD)		Mann-Whitney U test	Effect size r
						Males (N=40)	Females (N=20)		
Pleasant mood	3 (5.1)	4 (6.8)	9 (15.3)	22 (37.3)	21 (35.6)	4.1 (1)	3.6 (1.2)	U= 278.5	r= 0.22
Euphoria	2 (3.5)	8 (14)	11 (19.3)	16 (28.1)	20 (35.1)	4 (1.2)	3.3 (1.1)	U= 219.5*	r= 0.29
Ease	4 (7.1)	4 (7.1)	10 (17.9)	22 (39.3)	16 (28.6)	3.9 (1.1)	3.4 (1.3)	U= 266.5	r= 0.2
Tranquility	6 (10.3)	5 (8.6)	12 (20.7)	20 (34.5)	15 (25.9)	3.6 (1.3)	3.5 (1.2)	U= 334.5	r= 0.04
Feeling close to others	7 (12.1)	7 (12.1)	10 (17.2)	20 (34.5)	14 (24.1)	3.5 (1.3)	3.4 (1.3)	U= 342	r= 0.04
Feeling drunk	6 (10.2)	12 (20.3)	11 (18.6)	13 (22)	17 (28.8)	3.5 (1.4)	3.1 (1.4)	U= 319	r= 0.14
Stupor	3 (5.2)	11 (19)	18 (31)	16 (27.6)	10 (17.2)	3.4 (1.1)	3.1 (1.2)	U= 306	r= 0.13
Increased sexual arousal	10 (17.2)	14 (24.1)	7 (12.1)	12 (20.7)	15 (25.9)	3.2 (1.5)	3.1 (1.4)	U= 346.5	r= 0.03
Sharpened perception	9 (15.5)	12 (20.7)	13 (22.4)	14 (24.1)	10 (17.2)	3.2 (1.4)	2.8 (1.3)	U= 303	r= 0.15
Hyperactivity	13 (22.4)	9 (15.5)	14 (24.1)	16 (27.6)	6 (10.3)	3.2 (1.3)	2.3 (1.1)	U= 219*	r= 0.35

Notes: *p<0.05; **p<0.01; ***p<0.001

Participants were asked to provide information on the three most typical, three most beloved and three most adverse effects of GHB. In line with the above presented results, pleasant mood or joy (mentioned 33.5%), euphoria (26.7%), increased energy or activity (21.8%), relaxation or tranquility (10%), black-outs (10%) and various attributes of increased sociability (8.4%) were mentioned as most typical effects. Most beloved effects were pleasant mood (45.3%), increased energy (20.2%), euphoria (18.4%), relaxation (13.5%) and sociability (13.5%). Most frequently reported adverse effects were nausea or sickness (45%), black-outs (33.5%), vertigo (20.2%), fatigue or weakness (13.5%). Other adverse effects – such as headache, anxiety, disorientation, hangover, depression, deviant behavior, iirtability, bad taste, sweating and dehydration – were only mentioned by less than 10%. Sexual enhancement and sexual openness was mentioned among both the most typical and the most beloved effects of GHB, however, not among most adverse effects. Sexual enhancement and sexual openness were mentioned by 15% as most typical, and by 10% as most beloved effects.

Sexual effects

Specific sexual effects of GHB (Table 23) were also assessed. Every fourth respondents (25.4%) reported an intense attraction towards the sexual partner when using GHB. On the other hand, 84.5% said that they never had an unsatisfactory sexual experience when using GHB. Sexual disinhibition (28.8), heightened sense of touch (13.8), and more intense orgasms (12.3) were also relatively often experienced effects of GHB. Regarding gender differences, males more frequently experienced intense orgasms as a result of their GHB use. Except for the effect of sex being more boring under the influence of GHB, average daily dose (mg/day) showed significant and positive correlation with all specific sexual effects, indicating that those participants who never felt these effects, usually consumed lower doses of this substance.

Table 23. Specific sexual effects of GHB

	Never N (%)	Sometimes N (%)	Half of the cases N (%)	Most of the cases N (%)	Nearly always/ always N (%)	*Zero order Spearman correlations between sexual effects and average daily dose of GHB (mg/day)*
More intense attraction towards sexual partner	14 (23.7)	12 (20.3)	5 (8.5)	13 (22)	15 (25.4)	**0.54****
Sexual disinhibition	18 (30.5)	9 (15.3)	7 (11.9)	8 (13.6)	17 (28.8)	**0.49***
Heightened sense of touch (tactility)	15 (25.9)	11 (19)	10 (17.2)	14 (24.1)	8 (13.8)	**0.42***
More intense orgasm	27 (47.4)	8 (14)	7 (12.3)	8 (14)	7 (12.3)	**0.47***
Sex becomes more boring this way	49 (84.5)	5 (8.6)	3 (5.2)	0	1 (1.7)	0.15

Gender differences				
	Mean scale score (SD)		Mann Whitney U test	Effect size r
	Males (N=40)	Females (N=20)		
More intense attraction towards sexual partner	3.2 (1.6)	2.8 (1.5)	U= 325.5	r= 0.13
Sexual disinhibition	3.1 (1.7)	2.6 (1.5)	U= 317.5	r= 0.15
Heightened sense of touch (tactility)	2.9 (1.5)	2.7 (1.2)	U= 356.5	r= 0.07
More intense orgasm	2.7 (1.6)	1.6 (0.9)	U= 230*	r= 0.39
Sex becomes more boring this way	1.4 (0.9)	1.1 (0.2)	U= 317	r= 0.22

Notes: *p<0.05; **p<0.01; ***p<0.001. Significant correlations are boldfaced.

Choice of sexual partners

Results showed that more than half of the subjects (54.2%) do have sex under the influence of GHB, and 18.7% does so at least in the half of the cases. Interestingly, while 39.1% exlusively and another 19.6% most typically have sex with his/her partner when using GHB, others prefer to have sex with friends or even strangers under the influence of this substance (Table 24). Almost half of the respondents (44.8%) reported to have sex with friends or acquaintances when using GHB, and more than one third (34.5%) reported to do so with strangers. Establishing sexual intercourse with strangers under the influence of GHB was more common among males than females.

Table 24. Choice of sexual partners

		Gender differences		
		N (%)		Fisher's exact test
		Males (N=40)	Females (N=20)	
How often do you establish sexual intercourse under the influence of GHB?	Never	16 (40)	11 (55)	p=0.1291
	To a maximum of 10% of all the GHB use cases	3 (8)	4 (20)	
	10 to 40% of all the GHB use cases	10 (25)	4 (20)	
	50% or more than 50% of all the GHB use cases*	10 (25)	1 (5)	
With whom do you usually establish sexual intercourse under the influence of GHB?	Exclusively with my partner	9 (32)	9 (50)	p=0.6047
	Most typically with my partner but sometimes with other people	7 (25)	2 (11.1)	
	Most typically with friends or acquaintances	2 (7)	1 (5.6)	
	With those whom I meet at the time, even with strangers and with others*	10 (36)	6 (33.3)	
How often do you usually establish sexual intercourse with friends/acquaintances under the influence of GHB?	Never	17 (45)	15 (75)	p=0.1923
	Sometimes	12 (32)	3 (15)	
	Approximately in 50% of all the GHB use cases	3 (8)	1 (5)	
	Most of the GHB use cases or nearly always/always*	6 (15)	1 (5)	
How often do you usually establish sexual intercourse with strangers under the influence of GHB?	Never	20 (52.6)	18 (90)	p=0.0317
	Sometimes	8 (21.1)	1 (5)	
	Approximately in 50% of all the GHB use cases	4 (10.5)	1 (5)	
	Most of the GHB use cases*	6 (15.8)	0 (0)	

Notes: Two categories were collapsed in order to avoid empty cells.

Reasons and frequency of GHB use

The most frequently reported reason of GHB use was to reach an altered state of mind (reported by 25.9% as being a motive always or nearly always), where everything else ceases to be (17.2%), or to exclude everyday problems and situations (15.5%) (Table 25). Others frequently mentioned the need to 'recreate' (19%). With regard to the correlation between specific reasons of GHB use and the frequency of either last month use or self-reported mean dose of GHB, reaching an altered state of consciousness showed the highest correlation with self-reported mean dose of GHB. Though, 'enhancing sexual experience' was not an often reported reason of GHB use (only 3.4% mentioned this reason as being a motive of GHB use always or almost always), this reason showed the highest correlation with last month frequency of GHB use and a significant gender difference was found only in the case of this reason as males more frequently reported using GHB in order to enhance their sexual experience than females. Becoming more sociable and increasing self-confidence due to GHB consumption showed significant correlation with self-reported mean dose of GHB.

Table 25. Frequencies of GHB use and their correlations with potential reasons of use

Reasons of GHB use						Gender differences				*Zero order Spearman correlations between reasons and frequencies of GHB use*	
	Never N (%)	Some-times N (%)	Half of the cases N (%)	Most of the cases N (%)	Nearly always/ always N (%)	Mean scale score (SD) Males (N=40)	Females (N=20)	Mann-Whitney U test	Effect size r	Last month frequen-cy of use	Self-reported mean dose (mg)
To reach altered state of mind (%)	10 (17.2)	11 (19)	13 (22.4)	9 (15.5)	15 (25.9)	3.3 (1.4)	2.9 (1.6)	U= 343.5	r= 0.13	0.26	**0.73*****
To refreshen, recreate (%)	11 (19)	12 (20.7)	10 (17.2)	14 (24.1)	11 (19)	3.1 (1.5)	3 (1.3)	U= 372.5	r= 0.04	0.21	0.34
To exclude everyday problems (%)	19 (32.8)	10 (17.2)	9 (15.5)	11 (19)	9 (15.5)	2.7 (1.5)	2.8 (1.5)	U= 375.5	r= 0.03	0.08	0.11
Because everything else ceases to be (%)	19 (32.8)	10 (17.2)	12 (20.7)	7 (12.1)	10 (17.2)	2.7 (1.5)	2.6 (1.5)	U= 378	r= 0.03	0.02	0.21
To become more sociable (%)	19 (32.2)	15 (25.4)	9 (15.3)	8 (13.6)	8 (13.6)	2.7 (1.5)	2.1 (1.1)	U= 308	r= 0.22	**0.33***	**0.56****
To increase self-confidence (%)	25 (43.1)	9 (15.5)	7 (12.1)	10 (17.2)	7 (12.1)	2.7 (1.5)	1.9 (1.3)	U= 287	r= 0.27	0.21	**0.51****
To reduce tension and stress (%)	24 (41.4)	13 (22.4)	12 (20.7)	7 (12.1)	2 (3.4)	2.1 (1.1)	2.2 (1.3)	U= 383.5	r= 0.04	0.19	-0.02
To enhance sexual experience (%)	32 (55.2)	10 (17.2)	8 (13.8)	6 (10.3)	2 (3.4)	2.2 (1.3)	1.4 (0.6)	U=255.5*	r= 0.37	**0.41****	0.29

Notes: *p<0.05; **p<0.01; ***p<0.001

Being victimized, experiencing black-outs due to GHB use

Five subjects (8.6%) reported to be victims of acquisitory crimes, and two subjects (3.4%) reported to had suffered sexual assault, while one subject (1.7%) reported to had endured other crimes at least once in their lifetimes due to their GHB use. As a risk factor for being victimized in further sexual or acquisitory crimes, the frequency of experiencing black-outs due to GHB use was also assessed. 14 respondents (24.6%) experienced black-outs in at least half of their GHB use cases or more often.

7.6.4. Discussion

Sexual effects of GHB were listed among the most typical effects of this substance, indicating that these effects are indeed relevant sensations, when the daily dose of GHB increase. Sexual enhancement and sexual oppenness were also mentioned among the most sought-after effects of GHB, indicating that GHB might be popular for enhancing users' sexual life. Among the ten most frequently mentioned symptoms of GHB, we found both stimulant and depressant effects. This result can easily be explained by GHB's dose dependent characteristics as GHB might bind to GHB-specific receptor at low doses and by inhibiting presynaptic dopamine release it evokes stimulant-like effects (Maitre et al., 1990; Feigenbaum and Howard, 1996), while at higher doses, GHB stimulates $GABA_B$ receptor resulting in an increase in dopamine levels and inducing depressant effects (e.g. Xie and Smart, 1992; Nissbrandt and Engberg, 1996). GHB is thus often compared to both MDMA (Palamar and Halkitis, 2006; Lee and Levounis, 2008) – and sometimes even named as liquid ecstasy (e.g. Klein and Kramer, 2004; Barker et al., 2007) – and alcohol in it's subjective and neurotoxic effects (Barbaccia et al., 2002; Barker et al., 2007; van Amsterdam et al., 2012). On the other hand our result might implicate that GHB may effectively substitute both typical stimulant/entactogen subtsances – such as MDA or MDMA – and depressants – mainly such as alcohol. Futhermore, GHB seems to function as a stimulant substitute especially for males as they more frequently experience hyperactivity as a result of their GHB use.

Based on our findings, causing black-outs is also a marked property of GHB, with 14% experiencing black-outs nearly always or always and altogether 24% experiencing black-outs in at least half of their GHB use cases or more often. Black-out, which is, in our understanding, can be a risk factor for getting involved in unwanted sexual intercourses or enduring sexual or acquisitory crimes was also mentioned among the most typical effects of GHB. We found that 8.6% of the

sample suffered an acquisitory crime and 3.4% suffered a sexual assault at least once in their lifetimes due to their GHB use. Although our sample is not representative, the rate of 3.4% who endured a sexual assault may still be in line with the findings of former studies, in which GHB was detected in 0.2% to 5% of all reviewed sexual assaults (ElSohly and Salamone, 1999; Varela et al., 2004; Du Mont et al., 2010; Németh et al., 2010). Our results also indicate that suffering an acquisitory crime due to one's GHB consumption, might be a more frequently occuring phenomenon, with regard to both male and female GHB users. This is a phenomenon which needs further examination as GHB is almost exclusively linked to sexual assaults and both scientific papers and media reports tend to neglect the fact that victims of GHB involved crimes might be males as well. Since acquisitory crimes might be more easily carried out in discos and parties, one should assume that these offences occur more frequently.

When we specifically assessed sexual effects of GHB on the basis of former findings (Laborit, 1972; Miotto et al., 2001; Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008; Sumnall et al., 2008), we found that these sexual effects were mentioned by a high ratio of our respondents, which again confirms the relevance of GHB's effects on users' sexual experience. A more intense attraction towards the sexual partner was found to be the most typical sexual effect of this substance, with 47.4% reported to experience this effect in most of the cases or nearly always/always under the influence of GHB. Sexual disinhibition, increased tactility and more intense orgasm were also frequently occuring and potentially reinforcing effects with a possible impact on further and repeated GHB use as well. GHB's capability to boost orgasm seems to be more frequently experienced by males.

Regarding risky sexual behavior due to GHB use, we mainly assessed patterns of choice of sexual partners as this aspect was underexamined by other studies. High rates of our respondents reported to typically establish sexual intercourse under the influence of GHB, even with complete strangers or with friends but not with their partners. Establishing sexual intercourse with strangers while using psychoactive substances is already considered to be a serious risk factor for getting infected with various blood-borne diseases (e.g. Robertson and Plant, 1988; Castilla et al., 1999; Weidel et al., 2008). Males showed a more riskful choice of sexual partners while using GHB as establishing sexual intercourse with strangers was more common among them. Our result that sexual disinhibition is one of GHB's most typical sexual effect also needs to be taken into

consideration with regard to the role of GHB in risky sexual behavior. Additionally, GHB use itself had already been found to have a strong relation with both syphilis and HIV infection (Bellis et al., 2002).

The assessed reason to enhance sexual experiences by using GHB showed significant correlation with past month GHB use frequency. Based on this result, it can be suggested that although other reasons were more frequently reported by GHB users, the need to boost one's sexual life can be mentioned as one of the main risks for recurrent use. This is especially relevant among males who are more inclined to use GHB in order to enhance their sexual life. The intention to reach an 'altered state of mind' as the most frequently reported reason of GHB use showed the highest correlation with self-reported mean dose of GHB, indicating that this reason can be linked to a more harmful pattern of GHB use. Higher doses of GHB also showed significant correlation with the desires of being more sociable and self-confident utilizing the subjective effects of this substance.

The main limitation of our study lies in the relatively small sample size, although other studies on GHB use characteristics and sexual correlates of GHB use assessed similar or even smaller samples (e.g. Miotto et al., 2001; Barker er al., 2007; Lee and Levounis, 2008; Stein et al., 2011). Nevertheless, our sample size was unfortunately not suitable for multivariate statistics, yet it would be an important future research goal to explore potential classes of GHB users on a larger sample, using latent class analysis, based on users' preferences for either stimulant or depressant effects of GHB. A possible preference for GHB's depressant effects - e.g. tranquility, feeling drunk, stupor – would hypothetically be associated with higher doses and thus with more harmful GHB use, possibly attended by more frequent black-outs as well. Research has already demonstrated that GHB produces dose-related increases on users' subjective ratings regarding the effects of this substance (e.g. sedative, stimulant or dissociative effects) and drug liking (Oliveto et al., 2010). Another limitation which needs to be addressed is the fact that the effects of other substances consumed might lead to an attribution bias with regard to GHB's perceived effects. However, only an experimental design with controlled GHB intake would be appropriate for ruling out this kind of bias. Finally, we did not assess users' sexual orientation, which can also be mentioned as one of this study's limitations. The main strength of our study is due to the fact that we specifically focused on GHB's sexual effects and risky sexual behavioral correlates of the use of GHB.

8. DISCUSSION

8.1. Discussion of study results

The primary goal of my researches was to explore detailed characteristics of the use of NPSs in Hungary, including the psychosocial circumstances of the first and current use, the psychiatric profile of NPS users, the potential functions and reasons of the use of these drugs as well as their most frequently occuring subjective and somatic effects. The literature of NPSs is growing rapidly, although – with regard to my main research topics – it is still lacking sufficient empirical evidence, as one of the main danger of NPSs is the absence of knowledge about both the short-and long-term effects of these substances. As such, my researches shared an exploratory nature (see chapter 8.1.1.).

However, relying on the theoretical basis of three etiological models (self-medication; tramatic life events; social environment), the results of my researches are also interpreted (see chapter 8.1.2.) in a way that is testing the adaptability of these models regarding various characteristics of NPS use, as the second goal of my empirical work.

Therefore, in what follows, I discuss our findings in two separate section: Exploratory results (chapter 8.1.1.) and Testing theoretical assumptions (chapter 8.1.2.).

8.1.1. Exploratory results

8.1.1.1. Web search queries and NPSs

Our result that web interest on mephedrone is independent of the content of the published information and rather associated with the number of mephedrone being mentioned, holds important implications for drug prevention programs. This finding indicates that providing a) deterrent information and b) using only information delivery strategies in prevention might be a double-edged sword, as it may either provoke reluctance or even pique the target population's interest towards psychoactive substances. Former studies also emphasized potential disadvantages and ineffectiveness of providing only deterrent information in prevention programs (e.g. Rácz, 2000).

We found that web and indirectly social interest about mephedrone is less persistent than in the case of classic psychoactive substances. Web search queries therefore seem to be useful

indicators in predicting the popularity of NPSs, as – based on both clinical practice and addiction research – we know that illegitimate users' interest on NPS is rapidly forming. Unfortunately, in Hungary we do not have available data about the general population's mephedrone use prevalences. Hence, I could not test Google Trends's utility as an easy-to-use epidemiological indicator. However, as a future research goal, in collaboration with other treatment facilities (or the National Focal Point of Hungary), we might be able to explore further possibilities of using Google Trends in addiction research.

We demonstrated that legislative status of mephedrone predicts web interest on this substance. Most recently, Ledberg (2015) presented similar results, as he found that the activity on an internet discussion forum related to NPSs was significantly decreased around the time of classification. The impact of legislation regarding further NPSs needs to be tested with Google Trends as well, in order to find out to what extent this tool can be utilized. A potential function of Google Trends might be the analysis of time-dependent changes in the rates of web searches in relation to specific events (as an analogue for *event-related potential* in electroencephalography).

Considering the correlation between GHB-related web searches and the number of intoxications due to GHB overdose, Google Trends was found to be a promising indicator, even if only moderate correlation was observed between these variables. As another future research plan, in cooperation with Hungarian toxicology wards, the assessment of intoxication cases related to the overdose of various NPSs (registered in every month), could be correlated with web search queries regarding the same substances. Hence, we could get a clearer picture on the utility of Google Trends in NPS-related toxicology as a potential indicator of upcoming intoxications.

8.1.1.2. Mephedrone and other cathinones: substituting other substances

Substitutional potential of mephedrone was confirmed by our studies (7.2., 7.3., 7.4.). On the basis of its psychopharmacological effect, mephedrone can be a substitute for MDMA and other entactogen stimulants. Whereas on the basis of its intravenous administration, it can also function as a substitute for frequently injected drugs, such as amphetamines, cocaine or opioids.

Based on our findings, we can also interpret mephedrone use as a maladaptive coping strategy, as we found that those who perceive more intense subjective and somatic effects (i.e.

members of the second latent class) when taking mephedrone, may use this substance as an instrument to reduce stress. These users also consider mephedrone to be more addictive. In case of other psychostimulants, perceived effect intensity was linked to decreased cerebral blood flow in the right amygdala and hippocampus (Carhart-Harris et al., 2014), indicating not only psychological but also neurobiological differences between SUD individuals.

Injecting use of mephedrone and other cathinones was found to be a still existing problem, associated with riskful correlates, such as a higher average dose of mephedrone consumed, a more frequent monthly use of this substance, the consumption of other substances in order to ease mephedrone's adverse effects, a history of opioid use and more severe psychiatric symptoms. Our results, although not based on representative samples, may indicate that injecting cathinone use is a characteristic of opioid users, who formerly became addicted to injecting itself, which increases abuse liability and addictive potential of specific substances (e.g. Gossop et al., 1992; Hatsukami and Fischman, 1996; Strang et al., 1998; Volkow et al, 2000). The findings of Booth and colleagues (2006) also suggest that injection of any drug may be associated with more severe psychiatric symptoms, which again underlines the relevance of the route of administration in the severity of the assessed psychiatric symptoms.

8.1.1.3. GHB and sexuality

We aimed to raise awareness of GHB's use as both a recreational drug and a substance capable of increasing sexual desire and disinhibition by providing detailed and quantitative information on GHB's sexual effects and potential impact on choice of sexual partners. We also emphasized the risk of getting involved in unwanted sexual intercourses and thus getting infected with blood-borne diseases due to intentional use of GHB as a counter-example for enduring sexual violence due to unintentional intake of the same substance. Black-out as a marked property of intentional GHB intake also needs to be taken into consideration as a risk factor for suffering sexual or acquisitory crimes. The function of GHB as an effective substitute for both stimulant and depressant substances is also confirmed by our results, giving a plain explanation for GHB's remaining popularity.

Gender differences in both intentional and unwanted GHB intake need to be addressed as well. In line with former findings (e.g. Kim et al., 2007), male gender was found to be a risk factor

for experimenting with GHB's sexual enhancing effects and also for engaging in potentially riskful sexual activities. Futhermore, GHB was found to be a stimulant substitute especially for males as they more frequently reported hyperactivity as one of the relevant psychopharmacological effects of GHB. GHB's capability to increase the intensity of orgasm was also more inherent among males. Considering the involvement in GHB-facilitated crimes, male gender was also found to be a risk factor, indicating that in this case gender differences might be overemphasized, especially in media reports.

Based on our results, GHB's impact on human sexuality is considered to be a significant function of this substance. Intentional use of GHB seems to be more relevant than GHB being a date-rape drug, however, in line with former studies (e.g. Goullé et al., 2003), we also empirically proved that GHB is truly used as a roofie in some cases. As such, recent studies reported novel methods to detect GHB in various drinks, like the use of fluorescent sensor, which exhibits GHB's fluorescence quenching property (Zhai et al., 2014), or other color-change reagent tests that were also tested within real life circumstances (Quest and Horsley, 2007).

8.1.2. Testing theoretical assumptions

8.1.2.1. NPSs and self-medication

Our findings partially support but also contradict Khantzian's Self-Medication Hypothesis. Therefore, in the following, I systemitacally discuss these results.

Results that support the hypothesis:

Our multinomial regression analysis (7.3.) indicated that the severity of psychiatric symptoms predict mephedrone use frequency with an odds ratio of 2.95 to consume this NPS on either a weekly or daily basis, in comparison to occasional users. We also found that injectors of mephedrone with more severe psychiatric symptoms, tend to use mephedrone more regularly. Among opioid dependent patients (7.4.) we found that NPS – primarily synthetic cathinone - users are characterized by an elevated psychiatric symptom profile, in comparison to those patients who did not use NPSs. Finally, experiencing stressful life events, such as interpersonal conflicts, also predicted higher odds of using NPSs.

These findings confirm Khantzian's theory that SUD patients use various substances in order to medicate themselves. As already mentioned among the limitations of our studies, by using a cross-sectional design, we were unable to draw conclusions about the causality between NPS use and psychiatric symptoms. As we saw in our path analysis model (7.4.), the severity of psychiatric symptoms could also be interpreted as a mediator between NPS use and the perceived emotional intensity of interpersonal conflicts.

Results that contradict the hypothesis:

Among opioid dependent patients, we found that the severity of psychiatric symptom was not a signifant predictor of NPS use (7.4.). Furthermore, among the most frequently mentioned reasons of NPS use, we identified practical or even economical – like availability and substituting other drugs – and psychosocial reasons – like the impact of friends – and not psychopharmacological preferences.

Similarly, when we assessed potential reasons of GHB use among recreational users, we found that the reasons 'to reduce tension and stress' was one of the least frequently mentioned reason. This reason- which might be a potential way of self-medication – did not show significant association with GHB use frequencies either.

Based on these findings, we state that Khantzian's hypothesis is still one of the most relevant etiological model of substance use, however, we cannot fully support its utility regarding the etiological explanation of NPS use.

8.1.2.2. NPSs and traumatic life events

With regard to the impact of traumatic life events and related emotional reactivity, our results emphasize the relevance of distressing or even traumatic life situations in NPS use. Those life events of traumatic nature – i.e. the exposure to actual or threatened death, serious injury or sexual violation as described by DSM-5 (American Psychiatric Association, 2013) -, such as the loss of a child, the death of a partner or a relative, a suicide in the social environment evoked higher emotional intensity among SUD patients, compared to stressful but not traumatic life situtations, like divorce, break-up, retirement or job loss. In line with former findings that substance use may be associated with poorer living conditions as mediated by – among others - low educational level, early school leaving, unemployment, low salaries, insecurity of accommodation and social stigma (e.g. Waidner, 1999; DrugScope, 2000), a significant change in patients' living standards was found to be the most frequently occurring negative life event.

Gender was found to have a relevant impact on the perceived emotional intensity of the assessed life events. Being a female seems to be a significant risk factor regarding the emotional reactivity to interpersonal conflicts, pregnancy and parenting, illnesses and crime-related experiences. This result is also comparable to former findings (Breslau et al., 1997), indicating that women are more vulnerable to traumatic life events. In case of NPS using males, emotional reactivity to interpersonal conflicts was mediated by the severity of psychiatric symptoms, whereas psychiatric symptoms among female patients did not play a relevant role in the mediation between NPS use and emotional reactivity related to negative life events. This finding may denote that the neurobiological (e.g. Bianchin and Angrilli, 2012) and psychosocial (e.g. Bramston et al., 2000) differences between men and women in emotional sensitivity might be reduced by psychiatric symptoms. Aging also predicted higher emotional intensity as induced by relationship conflicts. Erik H. Erikson's model of psychosocial development (Erikson, 1950) may provide a potential explanation for this result. Given the fact that our sample consisted of opioid dependent patients with a mean age of 39.7 (SD=6.8), a significant proportion of our patients were in the sixth stage of Erikson's developmental model. Basic strength and goal of this stage, as described by Erikson,

is reaching intimacy and mutual sharing with another person. Therefore, we might presume that the older the patient is, the more important the relationship is to him/her and therefore becomes more upset if conflicts appear within the relationship. The connection between age and emotional reactivity was significant only among males. Hence, we may assume that age also reduce the above mentioned differences in emotional sensitivity between men and women. These gender differences may hold important implications for tailored interventions, developers of such programs are thus adviced to consider gender-related specificities.

8.1.2.3. Social environment of NPS use

Social context of both the onset and persisting NPS use was also proved to be an important factor. Furthermore, great similarities between mephedrone (7.3.) and GHB (7.6.) users were identified in psychocial factors and social environment of NPS use. Therefore, I mainly discuss our results in relation to NPS use in general and not separately by the characteristics of mephedrone and GHB use.

With regard to the onset of NPS use – the first encounter with the assessed NPSs – the impact of friends was found to be most relevant. Users most frequently tried NPSs with their acquintances for the first time, as well as they purchased NPSs from them, usually for free. Social context of NPS use remained similar in persisting NPS use. The significance of peers in NPS use was affirmed by others as well (e.g. Lea et al., 2011). Majority of our recreational NPS users – and not our opioid dependent patients – were in their twenties. As presented in the Introduction section of my thesis, others (e.g. Miotto et al., 2001; Degenhardt et al., 2003; Sumnall et al., 2008; Winstock and Marsden, 2010; Winstock et al., 2010; Carhart-Harris et al., 2011; Brunt et al., 2013) reported similar mean ages regarding user characteristics of NPSs. And as the impact of friends and acquintances on substance use is usually linked to adolescence and early adulthood (e.g. Maddahian et al., 1986; Nation and Heflinger, 2006), our results are comparable with former ones. Mean age of the first NPS use was around the age of 22. Based on this finding, we emphasize the importance of prevention programs for not just adolescents but young adults as well.

Easy availability of these NPSs clearly stands out from our findings as a high proportion of NPS users was still procuring the substance of abuse for free. As also described by former studies (e.g. Lee and Levounis, 2008), parties and clubs were the most significant recreational scenes of

both the onset and current NPS use. Therefore, we may presume, that users most typically consume NPSs during recreational events and share these substances with each other.

Slight differences occurred between mephedrone and GHB users. In case of mephedrone, the role of the internet as a potential source of purchase was more relevant than in the case of GHB. In comparison to the former findings of Dargan and colleagues (2010) and Matthews and Bruno (2010) who identified an approximate 10% of internet purchase among mephedrone users, our results indicate that online obtainment of mephedrone was less inherent. With regard to the reported locations of NPS use, house parties/hops were more frequently mentioned among GHB users. In terms of prevention, hops are hardly monitored, as it is a challenging if not impossible goal to conduct effective programs at these recreational events. Furthermore, these locations may help users in remaining a hidden population.

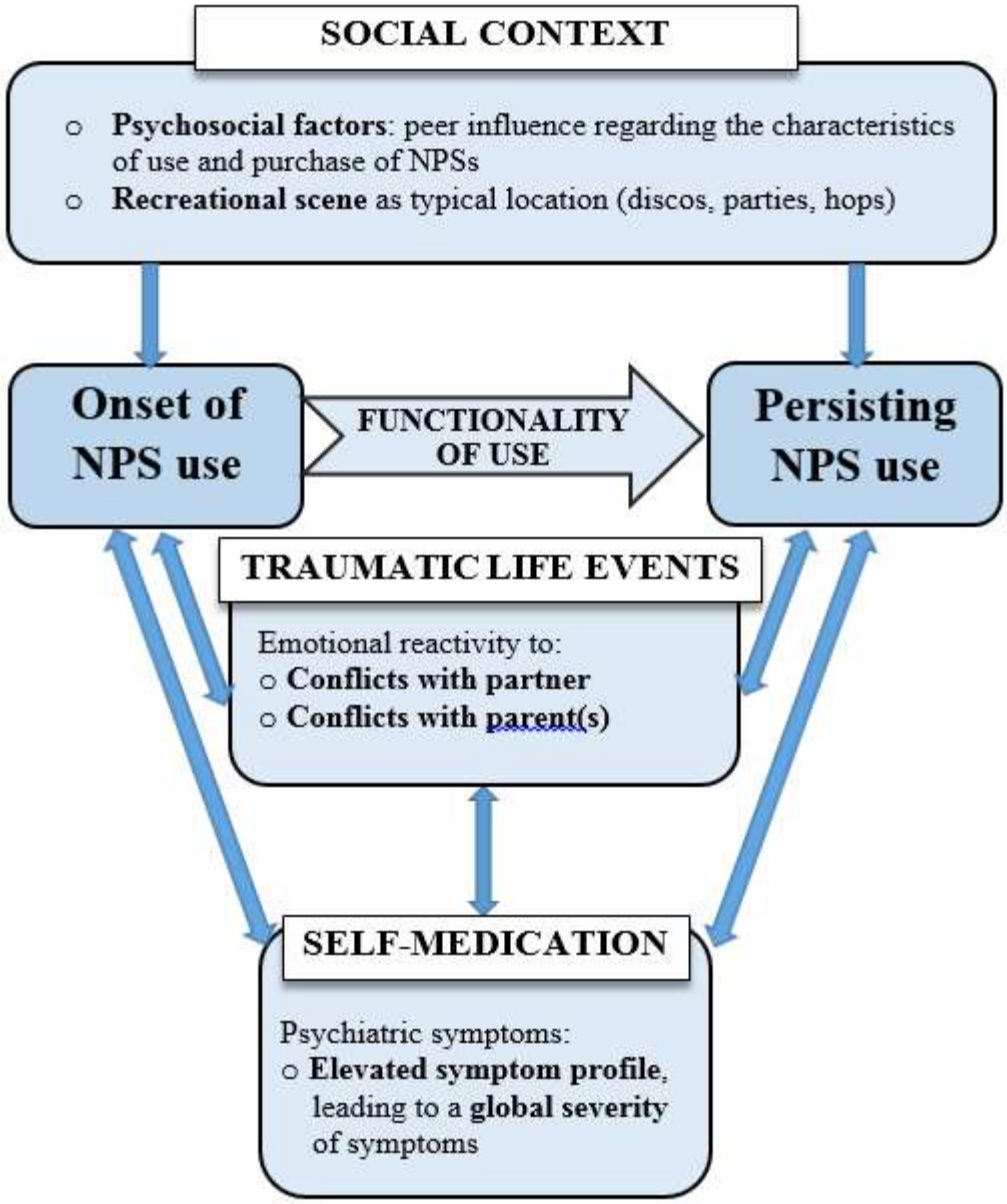
9. CONCLUSIONS

Some aspects of the functionality of NPSs were presented through our studies. These exploratory results may help in understanding a) the popularity and b) the hazardous consequences of NPS consumption. I consider injecting cathinone use, risky sexual correlates of GHB intake and the pattern of trying completely unknown substances to be the most harmful characteristics of this era of NPSs.

Interest towards NPS was indirectly observed in our first (7.1.) and fifth (7.5.) studies. We found that web interest towards mephedrone peaked in September 2010 and followed by its classification the rate of mephedrone-related web searches decreased. By assessing GHB-intoxicated patients and cases, we demonstrated that most of the cases occurred in 2011, followed by a decrease in such numbers. However, we also cited some recent studies (Brennan and Van Hout, 2014; van Amsterdam et al., 2014) that indicated GHB's and GBL's revolving popularity. Regarding synthetic cathinones, tenacious dominance of mephedrone has come to an end, its place was quickly taken over by similar cathinone-derivatives, such as MDPV and pentedrone as it was partially confirmed by our fourth study (7.4.). The market of classic psychoactive substances (e.g. heroin, cocaine, ecstasy) seems to be more viable. As we found in our first study (7.1.), the mean of overall web search query rates regarding these chemicals was significantly higher than in the case of mephedrone. This result denotes that after the zenith and disappearance of mephedrone, web interest towards these substances endured. Out of the assessed substances, cocaine-induced the most intense and coherent web interest (with the highest mean score). Geographic distribution of mephedrone-related web searches was centralized and restricted to Pest county and primarily Budapest. The location of web searches might be a useful indicator of the epidemiology of certain psychoactive substances, including NPSs. However, comparable data deriving from epidemiological research might be necessary for validating this novel research methodology.

As an effort to summarize our findings, I finally present an integrated model of the three cited psychological etiological theories, in relation to our results regarding the onset and persistence of NPS use (Figure 6).

Figure 6. Interrelatedness of tested theoretical assumptions in connection to the results of presented empirical researches



Considering both the onset and persistence of NPS use, psychosocial factors (mainly peer influence on the characteristics of use and purchase of NPSs) and the recreational scene as the setting for trying and later using NPS play a relevant role. Psychiatric symptoms, including the global severity of these symptoms showed correlational (two-sided) connection with both the onset and persisting use of NPSs. This association was interpreted as a supporting evidence for self-medication hypothesis, although the design of our studies did not allow us to confirm causality. Thus, vica versa, we might also presume that the use of NPSs can result in elevated psychiatric symptoms. Similarly, in case of the impact of negative life events, and emotional reactivity to them, these stressful experiences (emotional intensity as induced by interpersonal conflicts) were considered to either predict NPS use (in this case we did not differentiate between the onset and persistence of use, therefore we may hypothesize that negative life events have a significant impact on both), and NPS use was also tested as an explanatory variable for higher levels of emotional reactivity to these life situations. Furthermore the connection between NPS use and negative life events was found to be mediated by the severity of psychiatric symptoms among male opioid dependent patients.

I interpret the functionality of NPS use to play a significant role in persisting NPS use. In case of mephedrone and other synthetic cathinones, their capability to substitute various previously banned psychoactive substances, and in case of GHB, its sexually enhancing properies might have an impact on the persistence of NPS consumption.

10. FUTURE RESEARCH GOALS

10.1. Synthetic cannabinoids

As already mentioned in my foreword, our next research - related to NPS use - about various aspects of synthetic cannabinoid use is yet to be finished. With permission of the Research Ethical Committee of the Nyírő Gyula Hospital - National Institute of Psychiatry and Addictions, this is an ongoing study, started in May 2015.

The primary goals of this research is to compare synthetic cannabinoids (*bioweed* products) with cannabis in terms of subjective effects, correlated psychiatric symptoms, reasons of use and cognitive impairment related to the consumption of these substances. Both former finding by others (e.g. Castellanos et al., 2011; Vandrey et al., 2012; Winstock and Barratt, 2013) and our own results (Kapitány-Fövény et al., 2013b) on subjective and somatic effects and most frequently reported reasons of synthetic cannabinoid use were utilized in developing our questionnaire.

Finally, in relation to clinically observed psychotic states of synthetic cannabinoid users, dissociative experiences will also be assessed and compared between cannabis and synthetic cannabinoid users.

This study is in line with our researches presented in this thesis.

10.2. Development of interactive prevention tools

I also aim to utilize the findings of our studies by developing interactive prevention tools of easy online availability. Smartphone-and web-based interventions provide an opportunity to access addicted individuals who may be in the early stage of their mental health problem and who otherwise might not seek professional help. Users of illicit substances and NPSs especially show a high risk of remaining a hidden and therefore untreated population. For such hidden groups, the anonymity and accessibility of the Internet often leads to increased self-disclosure in sensitive areas such as substance abuse or risky sexual behavior (Turner et al., 1998). The result that tailored and interactive sites are more effective than static ones (Civljak et al., 2010) is essential regarding our proposed project. This project is titled: Click to Heal! (~ Kattanj rá! in Hungarian).

In cooperation with colleagues from Hungary (ELTE and SE), Germany (Institute for Therapy Research), the United Kingdom (University of Hertfordshire) and Romania (Babeş-Bolyai University), we submitted a grant proposal (H2020) for developing an interactive portal for both prevention, intervention and research purposes. The planned portal will consists of four modules: 1) *Knowledge module* (provides information about substance use and behavioral addictions in an interactive way); 2) *Life-path predictor* (computer based predictive models about relevant life events of SUD individuals as well as an interactive role playing game that support decision making of addicted individuals); 3) *Intervention module* (including web-based cognitive behavioral therapy and motivational enhancement therapy) and 4) *Discussion module* (aims to create an online platform for building self-help communities).

The development of these modules will be based on the overview of the current literature of addiction research, including our findings regarding NPS use and its correlates.

Web-based interventions such as this are considered to be innovative and cost-effective (they are delivered to large numbers without real therapist time). As opposite to face-to-face interventions, self-directed methods overcome geographical, temporal or financial burdens (Abbott et al., 2008). We expect our website to be an effective therapeutic tool for those who manage to become and remain abstinent or asymptomatic without face-to-face psychotherapy and pharmacotherapy. An effectiveness and cost-effectiveness study will be part of this project. Data will be collected through the intervention phase. We expect to confirm cost-effectiveness of such a web-based intervention as it was found in different public health contexts (Golsteijn et al., 2014) and in treating addictive behaviours (Smit et al, 2013).

This platform will also provide an opportunity to collect data about current self-management practices of SUD and those with behavioral addictions, as well as on unknown aspects, such as visitors' reports on the price, on the consumption methods or on the adverse effects of NPSs, within the confines of the Discussion module.

Alongside with the proposal regarding the above mentioned portal, another grant proposal was submitted recently to the National Institute for Family and Social Policy of Hungary with my colleagues from the drug outpatient centre of the Nyírő Gyula Hospital - National Institute of Psychiatry and Addictions. In case of this proposal, we aim to develop a smartphone-based interactive prevention tool (application) for adolescents and their parents. This project is titled: Once upon a drug (~Egy Szer Volt in Hungarian).

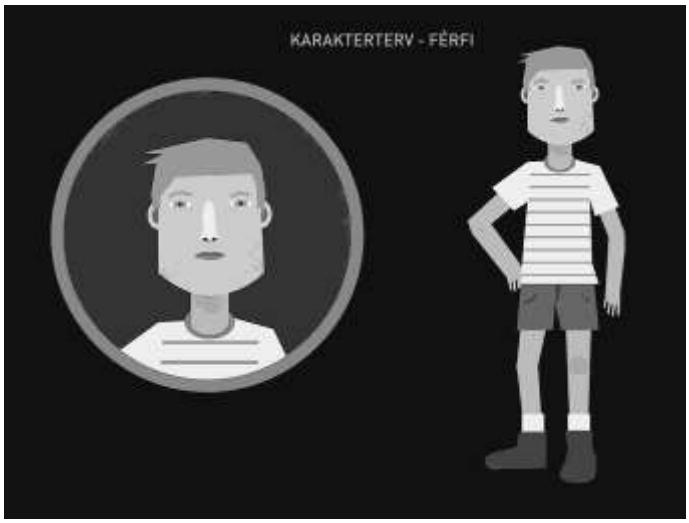
The application for adolescents will consists of the following modules:

a) *Once upon a drug*: recovery stories based on the findings of qualitative studies (e.g. Rácz, 2006), with interactive animations. Protective and risk factors of both SUD and the recovery process will be presented through these stories.

b) Beliefs: demonstration of common beliefs and misbeliefs about psychoactive substances, including NPSs. Information based on former studies (e.g. Hibell et al., 2012) will be presented through quiz-like questions and answers.

c) *Morphosis*: adverse effects of various substances, including NPSs will be presented by demonstrating somatic changes in either a male (Figure 7) or a female body.

Figure 7. Visual sample of a male body to be morphed by the somatic effects of the selected substances



Note: The visual sample was designed by Lukács Lívia

d) *What if?*: a hypothetical situation will be described about the substance use of a beloved person (e.g. family member, friend, partner, etc.). The adolescents will be asked to give effective advices to this person, in order to help him/her in stop using psychoactive substances. The answers of the adolescent will be registered by the application and as a feedback it will also be presented later on to the adolescent himself/herself.

e) *Alternatives*: potential alternatives of substance use will be presented in line with the introduction of various reasons of substance use (e.g. reason: to reduce stress-alternative: to try a relaxation technique)

f) *Where can I get help?*: self-report screening instuments will be made available for the adolescents. After giving a feedback on the results of the test, the application will present contact details of available treatment services not only in Budapest, but in the whole country.

<u>The application for the parents will will consists of the following modules</u>:

a) *Signs*: potential signs of substance use and withdrawal will be presented alongside with useful information that might help in differentiating between substance use-related problems and similar states caused by other factors. The aim of this differentiation is to minimize stigmatization and libel.

b) Family and substance: with the help of interactive animation and graphics, information will be provided on the family dynamics of substance use and potential roles of the family members in it. As part of this module, an animated tool will help the parents in identifying frequent cognitions and affects deriving as a result of the adolescent's substance use. Psychoeducative support will be provided in order to decrease the level of fear, anxiety, shame and guilt.

c) *Where can I get help?*: contact details of available treatment centres and parent groups will be presented.

11. REFERENCES

Aarde, S.M., Angrish, D., Barlow, D.J., Wright Jr, M.J., Vandewater, S.A., Creehan, K.M., Houseknecht, K.L., Dickerson, T.J., Taffe, M.A. (2013). Mephedrone (4-methylmethcathinone) supports intravenous self-administration in Sprague-Dawley and Wistar rats. *Addiction Biology,* 18 (5): 786-799.

Abbott, J., Klein, B., Ciechomski, L. (2008). Best practices in online therapy. *Journal of Technology in Human Services*, 26 (2-4): 360–375.

Adamowicz, P., Tokarczyk, B., Stanaszek, R., Slopianka, M. (2013). Fatal mephedrone intoxication - A case report. *Journal of Analytical Toxicology,* 37 (1): 37-42.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.).* Washington, DC: American Psychiatric Association

Anderson, I.B., Kim, S.Y., Dyer, J.E., Burkhardt, C.B., Iknoian, J.C., Walsh, M.J., Blanc, P.D. (2006). Trends in γ-Hydroxybutyrate (GHB) and Related Drug Intoxication: 1999 to 2003. *Annals of Emergency Medicine*, 47 (2): 177-183.

Andrássy, G., Asztalos, Z., Égerházi, A., Frecska, E. (2013). Observations of MDPV users: a prospective-retrospective study. *Psychiatria Hungarica*, 28(2): 189-194.

Angelone, D.J., Mitchell, D., Pilafova, A. (2007). Club drug use and intentionality in perceptions of rape victims. *Sex Roles*, 57 (3-4): 283-292.

Anglin, D., Spears, K.L., Hutson, H.R. (1997). Flunitrazepam and its involvement in date or acquaintance rape. *Academic Emergency Medicine*, 4 (4): 323–326.

Araújo, A.M., Valente, M.J., Carvalho, M., Dias da Silva, D., Gaspar, H., Carvalho, F., de Lourdes Bastos, M., Guedes de Pinho, P. (2015). Raising awareness of new psychoactive substances: chemical analysis and in vitro toxicity screening of 'legal high' packages containing synthetic cathinones. *Archives of Toxicology*, 89 (5): 757-771.

Arpawong, T.E., Sussman, S., Milam, J.E., Unger, J.B., Land, H., Sun, P., Rohrbach, L.A. (2015). Post-traumatic growth, stressful life events, and relationships with substance use behaviors among alternative high school students: a prospective study. *Psychology & Health*, 30(4): 475-494.

Badour, C.L., Feldner, M.T. (2013). Trauma-related reactivity and regulation of emotion: associations with posttraumatic stress symptoms. *Journal of Behavior Therapy and Experimental Psychiatry*, 44(1): 69-76.

Bajaj, N., Mullen, D., Wylie, S. (2010). Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. *BMJ Case Reports*, 2010: bcr0220102780. doi:

Barbaccia, M.L., Colombo, G., Affricano, D., Carai, M.A., Vacca, G., Melis, S., Purdy, R.H., Gessa, G.L. (2002). $GABA_B$ receptor-mediated increase in neurosteroids by gamma-hydroxybutyric acid. *Neuropharmacology*, 42 (6): 782 -791.

Barker, J.C., Harris, S.L., Dyer, J.E. (2007). Experiences of gamma hydroxybutyrate (GHB) ingestion: a focus group study. *Journal of Psychoactive Drugs*, 39 (2): 115-129

Bellis, M., Cook, P., Clark, P., Syed, Q., Hoskins, A. (2002). Re-emerging syphilis in gay men: a case-control study of behavioural risk factors and HIV status. *Journal of Epidemiology and Community Health*, 56 (3): 235–236.

Bessman, S.P., Fishbein, W.N. (1963). Gamma-Hydroxybutyrate, a Normal Brain Metabolite. *Nature*, 200: 1207-1208.

Bianchin, M., Angrilli, A. (2012). Gender differences in emotional responses: a psychophysiological study. *Physiology & Behavior*, 105(4): 925-932.

Blum, K., Cull, J.G., Braverman, E.R., Comings, D.E. (1996). Reward deficiency syndrome. *American Scientist*, 84: 132-145.

Bodmer, M., Enzler, F., Liakoni, E., Bruggisser, M., Liechti, M.E. (2014). Acute cocaine-related health problems in patients presenting to an urban emergency department in Switzerland: a case series. *BMC Research Notes*, 7: 173.

Booth, B., Leukefeld, C., Falck, R., Wang, J., Carlson, R. (2006). Correlates of rural methamphetamine and cocaine users: Results from a multisite community study. *Journal of Studies on Alcohol* 67(4): 493−501.

Booth, R.E. (2013). 'Krokodil' and other home-produced drugs for injection: a perspective from Ukraine. *The International Journal on Drug Policy*, 24(4): 277-278.

Borek, H.A., Holstege, C.P. (2012). Hyperthermia and multiorgan failure after abuse of "bath salts" containing 3,4-methylenedioxypyrovalerone. *Annals of Emergency Medicine*, 60 (1): 103-105.

Botescu, A., Abagiu, A., Mardarescu, M., Ursan, M. (2012). *HIV/AIDS among injecting drug users in Romania: report of a recent outbreak and initial response policies*. European Monitoring Centre for Drugs and Drug Addiction, Lisbon, November.

Boys, A., Marsden, J., Griffiths, P., Fountain, J., Stillwell, G., Strang, J. (1999). Substance use among young people: the relationship between perceived functions and intentions. *Addiction*, 94(7): 1043-1050.

Brady, K.T., Dansky, B.S., Back, S.E., Foa, E.B., Carroll, K.M. (2001). Exposure therapy in the treatment of PTSD among cocaine-dependent individuals: preliminary findings. *Journal of Substance Abuse Treatment*, 21(1): 47-54.

Bramston, P., Rogers-Clark, C., Hegney, D., Bishop, J. (2000). Gender roles and geographic location as predictors of emotional distress in Australian women. *The Australian Journal of Rural Health*, 8(3): 154-160.

Brennan, R., Van Hout, M.C. (2014). Gamma-hydroxybutyrate (GHB): a scoping review of pharmacology, toxicology, motives for use, and user groups. *Journal of Psychoactive Drugs*, 46(3): 243-251.

Breslau, N., Davis, G.C., Andreski, P., Peterson, E.L., Schultz, L.R. (1997). Sex differences in posttraumatic stress disorder. *Archives of General Psychiatry*, 54(11): 1044-1048.

Bright, S.J., Bishop, B., Kane, R., Marsh, A., Barratt, M.J. (2013). Kronic hysteria: Exploring the intersection between Australian synthetic cannabis legislation, the media, and drug-related harm. *The International Journal on Drug Policy*, 24 (3): 231-237.

Broughton, R., Mamelak, M. (1979). The treatment of narcolepsy-cataplexy with nocturnal GHB. *The Canadian Journal of Neurological Sciences*, 6 (1): 1-6.

Brunt, T.M., Koeter, M.W., Hertoghs, N., van Noorden, M.S., van den Brink, W. (2013). Sociodemographic and substance use characteristics of gamma hydroxybutyrate (GHB) dependent inpatients and associations with dependence severity. *Drug and Alcohol Dependence*, 131(3): 316-319.

Brunt, T.M., Poortman, A., Niesink, R. J. M., van den Brink, W. (2011). Instability of the ecstasy market and a new kid on the block: mephedrone. *Journal of Psychopharmacology*, 25 (11): 1543-1547.

Buchanan, J.F., Brown, C.R. (1988). 'Designer drugs'. A problem in clinical toxicology. *Medical Toxicology and Adverse Drug Experience*, 3 (1): 1-17.

Bullock, C.M., Beckson, M. (2011). Male victims of sexual assault: phenomenology, psychology, physiology. *The Journal of the American Academy of Psychiatry and the Law*, 39 (2): 197-205.

Cameron, K.N., Kolanos, R., Solis, E. Jr, Glennon, R.A., De Felice, L.J. (2013). Bath salts components mephedrone and methylenedioxypyrovalerone (MDPV) act synergistically at the human dopamine transporter. *British Journal of Pharmacology*, 168 (7): 1750-1757.

Camilleri, A., Johnston, M. R., Brennan, M., Davis, S., Caldicott, D. G. (2010). Chemical analysis of four capsules containing the controlled substance analogues 4-methylmethcathinone, 2-fluoromethamphetamine, alpha-phthalimidopropiophenone and N-ethylcathinone. *Forensic Science International*, 197 (1-3): 59–66.

Caputo, F., Vignoli, T., Maremmani, I., Bernardi, M., Zoli, G. (2009). Gamma hydroxybutyric acid (GHB) for the treatment of alcohol dependence: a review. *International Journal of Environmental Research and Public Health*, 6(6): 1917-1929.

Carhart-Harris, R.L., King, L.A., Nutt, D.J. (2011). A web-based survey on mephedrone. *Drug and Alcohol Dependence*, 118 (1): 19-22.

Carhart-Harris, R.L., Murphy, K., Leech, R., Erritzoe, D., Wall, M.B., Ferguson, B., Williams, L.T., Roseman, L., Brugger, S., De Meer, I., Tanner, M., Tyacke, R., Wolff, K., Sethi, A., Bloomfield, M.A., Williams, TM., Bolstridge, M., Stewart, L., Morgan, C., Newbould, R.D., Feilding, A., Curran, H.V., Nutt, D.J. (2014). The Effects of Acutely Administered 3,4-Methylenedioxymethamphetamine on Spontaneous Brain Function in Healthy Volunteers Measured with Arterial Spin Labeling and Blood Oxygen Level-Dependent Resting State Functional Connectivity. *Biological Psychiatry*. doi: 10.1016/j.biopsych.2013.12.015.

Castellanos, D., Singh, S., Thornton, G., Avila, M., Moreno, A. (2011). Synthetic cannabinoid use: a case series of adolescents. *The Journal of Adolescent Health*, 49 (4): 347–349.

Castilla J, Barrio G, Belza MJ, de la Fuente L. (1999). Drug and alcohol consumption and sexual risk behaviour among young adults: results from a national survey. *Drug and Alcohol Dependence*, 56 (1): 47-53.

Center for Substance Abuse Treatment (2004). *Substance Abuse Treatment and Family Therapy*. Treatment Improvement Protocol (TIP) Series, No. 39. DHHS Publication No. (SMA) 04-3957. Rockville, MD: Substance Abuse and Mental Health Services Administration.[Online] Available: http://www.ncbi.nlm.nih.gov/books/NBK64269/

Chan, E.H., Sahai, V., Conrad, C., Brownstein, J.S. (2011). Using web search query data to monitor dengue epidemics: a new model for neglected tropical disease surveillance. *PLoS Neglected Tropical Diseases*, 5(5): e1206.

Cheng, W.S., Garfein, R.S., Semple, S.J., Strathdee, S.A., Zians, J.K., Patterson, T.L. (2010). Increased drug use and STI risk with injection drug use among HIV-seronegative heterosexual methamphetamine users. *Journal of Psychoactive Drugs,* 42 (1): 11-18.

Chin, R.L., Sporer, K.A., Cullison, B., Dyer, J.E., Wu, T.D. (1998). Clinical course of gamma-hydroxybutyrate overdose. *Annals of Emergency Medicine*, 31 (6):716-722.

Choudhuri, D., Cross, S., Dargan, P.I., Wood, D.M., Ranjith, G. (2013). Psychiatric aspects of acute withdrawal from gamma-hydroxybutyrate (GHB) and its analogue gamma-butyrolactone (GBL): implications for psychiatry services in the general hospital. *International Journal of Psychiatry in Clinical Practice*, 17(2): 154-156.

Civljak, M., Sheikh, A., Stead, L.F., Car, J. (2010). Internet-based interventions for smoking cessation. *The Cochrane Database of Systematic Reviews*, 9: CD007078. doi: 10.1002/14651858.

Coffey, S.F., Schumacher, J.A., Stasiewicz, P.R., Henslee, A.M., Baillie, L.E., Landy, N. (2010). Craving and physiological reactivity to trauma and alcohol cues in posttraumatic stress

disorder and alcohol dependence. *Experimental and Clinical Psychopharmacology*, 18(4): 340-349.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (*2nd ed.*). Hillsdale, NJ: Erlbaum.

Collins, L. M., Lanza, S. T. (2010). *Latent class and latent transition analysis for the social, behavioral, and health sciences*. New York: Wiley.

Corazza, O., Valeriani, G., Bersani, F.S., Corkery, J., Martinotti, G., Bersani, G., Schifano, F. (2014). "Spice," "kryptonite," "black mamba": an overview of brand names and marketing strategies of novel psychoactive substances on the web. *Journal of Psychoactive Drugs*, 46 (4): 287-294.

Cottencin, O., Rolland, B., Karila, L. (2014). New designer drugs (synthetic cannabinoids and synthetic cathinones): review of literature. *Current Pharmaceutical Design*, 20 (25): 4106-4111.

Couper, F.J., Marinetti, L.J. (2002). γ-Hydroxybutyrate (GHB) — Effects on human performance and behavior. *Forensic Science Review*, 14 (1-2), 1-21.

Couper, F.J., Thatcher, J.E., Logan, B.K. (2004). Suspected GHB overdoses in the emergency department. *Journal of Analytical Toxicology*, 28 (6): 481-484.

Csák, R., Demetrovics, Zs., Rácz, J. (2013). Transition to injecting 3,4-methylene-dioxy-pyrovalerone (MDPV) among needle exchange program participants in Hungary. *Journal of Psychopharmacology*, 27(6): 559-563.

Dackis, C. A., Gold, M. S. (1986). More on self-medication and drug abuse. *American Journal of Psychiatry, 143*(10): 1309–1310.

Dargan, P.I., Albert, S., Wood, D.M. (2010). Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *The Quarterly Journal of Medicine*, 103 (11), 875–879.

Darke, S., Kaye, S. (2004). Attempted suicide among injecting and noninjecting cocaine users in Sydney, Australia. *Journal of Urban Health*, 81 (3): 505–515.

Davies, C., English, L., Lodwick, A., McVeigh, J., Bellis, M.A. (eds.). (2010). *United Kingdom Drug Situation: Annual Report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2010*. United Kingdom, Department of Health, United Kingdom Focal Point on Drugs

Davison, D., Parrott, A. C. (1997). Ecstasy (MDMA) in recreational users: self-reported psychological and physiological effects. *Human Psychopharmacology*, 12 (3): 221-226.

Degenhardt, L., Darke, S., Dillon, P. (2003). The prevalence and correlates of gamma-hydroxybutyrate (GHB) overdose among Australian users. *Addiction*, 98 (2): 199-204.

Degenhardt, L., Dunn, M. (2008). The epidemiology of GHB and ketamine use in an Australian household survey. *International Journal of Drug Policy*, 19 (4): 311-316.

Demetrovics, Zs. (2005). A rekreációs környezetben megjelenő droghasználat alakulása Magyarországon. In: Borsi É., Portörő P. (szerk.). *Jelentés a magyarországi kábítószerhelyzetről 2005*. Ifjúsági, Családügyi, Szociális és Esélyegyenlőségi Minisztérium, Budapest, pp. 81–98.

Demetrovics, Zs. (2007). *A droghasználat funkciói*. Akadémiai Kiadó, Budapest.

Demetrovics, Zs., Kun, B., Nádas, E., Vadász, P. (2008). A magyarországi táncos-zenés rekreációs színtéren megjelenő droghasználat jellemzői. In Demetrovics, Zs., Rácz, J. (szerk). *Partik, drogok, ártalomcsökkentés- Kvalitatív kutatások a parti-szcénában*. L'Harmattan, Budapest, pp. 25-224.

den Hollander, B., Rozov, S., Linden, A.M., Uusi-Oukari, M., Ojanperä, I., Korpi, E.R. (2013). Long-term cognitive and neurochemical effects of "bath salt" designer drugs methylone and mephedrone. *Pharmacology, Biochemistry, and Behavior*, 103(3): 501-509.

Derogatis, L.R. (1975). *Brief Symptom Inventory*. Baltimore, MD: Clinical Psychometric Research

Derogatis, L.R. (1993) *BSI Brief Symptom Inventory. Administration, Scoring, and Procedures Manual. 4th edition*. Minneapolis, MN: National Computer Systems

Dick, D., Torrance, C. (2010). 'MixMag Drugs Survey'. *Mix Mag 225*, 44-53.

Dickson, A.J., Vorce, S.P., Levine, B., Past, M.R. (2010). Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. *Journal of Analytical Toxicology,* 34 (3): 162-168.

Dijkstra, B.A.G., de Weert van Oene, G., Verbrugge, C.A.G., De Jong, C.A.J. (2013). *GHB Detoxificatie met Farmaceutische GHB. Eindrapportage van de Monitoring van DeTiTap in de Nederlandse verslavingszorg*. NISPA, Nijmegen. [Online] Available: http://www.nispa.nl/en/nieuws

Domier, C.P., Simon, S.L., Rawson, R.A., Huber, A., Ling, W. (2000). A comparison of injecting and noninjecting methamphetamine users. *Journal of Psychoactive Drugs,* 32 (2): 229–232.

Donovan, B., Padin-Rivera, E., Kowaliw, S. (2001). "Transcend": initial outcomes from a posttraumatic stress disorder/substance abuse treatment program. *Journal of Traumatic Stress*, 14(4): 757-772.

Downing, J. (1986). The psychological and physiological effects of MDMA on normal volunteers. *Journal of Psychoactive Drugs,* 18 (4): 335–340.

Dragogna, F., Oldani, L., Buoli, M., Altamura, A. C. (2014). A case of severe psychosis induced by novel recreational drugs. *F1000Research*, 3:21, doi: 10.12688/f1000research.3-21.v1

Dresen, S., Ferreirós, N., Pütz, M., Westphal, F., Zimmermann, R., Auwärter, V. (2010). Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *Journal of Mass Spectrometry*, 45(10): 1186-1194.

DrugScope (2000). *Vulnerable Young People and Drugs: Opportunities to Tackle Inequalities*. DrugScope: London.

DrugScope (2012). Druglink Street Drug Trends Survey 2012. *DrugLink November/December 2012*. [Online] Available: http://www.drugscope.org.uk/Resources/Drugscope/Documents/PDF/Publications/StreetDrugTrendsSurvey.pdf

Du Mont, J., Macdonald, S., Rotbard, N., Bainbridge, D., Asllani, E., Smith, N., Cohen, M.M. (2010). Drug-facilitated sexual assault in Ontario, Canada: toxicological and DNA findings. *Journal of Forensic and Legal Medicine,* 17 (6): 333-338.

El-Bassel, N., Gilbert, L., Wu, E., Go, H., Hill, J. (2005). Relationship between drug abuse and intimate partner violence: a longitudinal study among women receiving methadone. *American Journal of Public Health*, 95(3): 465-470.

Elekes, Zs. (2012). *Droghasználat iskolában tanuló fiatalok körében – ESPAD 2011*. Kézirat

ElSohly, M.A., Salamone, S.J. (1999). Prevalence of drugs used in cases of alleged sexual assault. *Journal of Analytical Toxicology*, 23 (3): 141–146.

EMCDDA (2008). GHB *and its precursor GBL: an emerging trend case study*. [Online] Available: http://www.emcdda.europa.eu/publications/thematic-papers/ghb

EMCDDA (2010). *Drugnet Europe 70*. EMCDDA: Lisbon ISSN 0873-5379.

EMCDDA (2011a). *Annual Report 2011: The state of the Drugs Problem in Europe*. Publications Office of the European Union: Luxembourg.

EMCDDA (2011b). *Joint EMCDDA and ECDC rapid risk assessment. HIV in injecting drug users in the EU/EEA, following a reported increase of cases in Greece and Romania*. Luxembourg: Publications Office of the European Union.

EMCDDA (2012). *Annual Report 2012: The state of the drugs problem in Europe*. Luxembourg: Publications Office of the European Union.

EMCDDA (2014a). *Perspectives on drugs: Injection of synthetic cathinones*. [Online] Available: http://www.emcdda.europa.eu/topics/pods/synthetic-cathinones-injection

EMCDDA (2014b). *European Drug Report 2014: Trends and developments*. [Online] Available: http://www.emcdda.europa.eu/publications/edr/trends-developments/2014

EMCDDA (2015). *New psychoactive substances in Europe. An update from the EU Early Warning System (March 2015)*. Luxembourg: Publications Office of the European Union. [Online] Available: http://www.emcdda.europa.eu/publications/2015/new-psychoactive-substances

Erikson, E. H. (1950). *Childhood and Society*. New York, NY: W.W.Norton & Company.

European Commission (2008). *Young people and drugs among 15-24 year-olds*. Flash EB Series #233. European Commission, Dublin: Ireland.

Europol-EMCDDA (2010). *Joint Report on a new psychoactive substance: 4-Methylmethcathinone (mephedrone)*. Luxembourg: Publications Office of the European Union.

Faravelli, C., Catena, M., Scarpato, A., Ricca, V. (2007). Epidemiology of life events: life events and psychiatric disorders in the Sesto Fiorentino study. *Psychotherapy and Psychosomatics*, 76(6): 361-368.

Fattore, L., Fratta, W. (2011). Beyond THC: The New Generation of Cannabinoid Designer Drugs. *Frontiers in Behavioral Neuroscience*, 5: 60. doi: 10.3389/fnbeh.2011.00060.

Feigenbaum, J.J., Howard, S.G. (1996). Does gamma-hydroxybutyrate inhibit or stimulate central DA release? *The International Journal of Neuroscience*, 88 (1-2): 53-69.

Fendrich, M., Wislar, J.S., Johnson, T.P., Hubbell, A. (2003). A contextual profile of club drug use among adults in Chicago. *Addiction*, 98(12): 1693-1703.

Forsyth, A.J.M. (2012). Virtually a drug scare: Mephedrone and the impact of the Internet on drug news transmission. *The International Journal on Drug Policy*, 23 (3): 198-209.

Frances, R. J. (1997). The wrath of grapes versus the self-medication hypothesis. *Harvard Review of Psychiatry, 4*(5): 287–289.

Franken, I.H., Hendriks, V.M., Haffmans, P.M., van der Meer, C.W. (2001). Coping style of substance-abuse patients: effects of anxiety and mood disorders on coping change. *Journal of Clinical Psychology*, 57(3): 299-306.

Freeman, T. P., Morgan, C. J., Vaughn-Jones, J., Hussain, N., Karimi, K., Curran, H. V. (2012). Cognitive and subjective effects of mephedrone and factors influencing use of a 'new legal high'. *Addiction*, 107 (4): 792-800.

Friedman, J., Westlake, R., Furman, M. (1996). "Grievous bodily harm:" gamma hydroxybutyrate abuse leading to a Wernicke-Korsakoff syndrome. *Neurology*, 46(2): 469-471.

Gallimberti, L., Canton, G., Gentile, N., Ferri, M., Cibin, M., Ferrara, S.D., Fadda, F., Gessa, G.L. (1989). Gamma-hydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet*, 334 (8666): 787–789.

Gallimberti, L., Cibin, M., Pagnin, P., Sabbion, R., Pani, P.P., Pirastu, R., Ferrara, S.D., Gessa, G.L. (1993). Gamma-hydroxybutyric acid for treatment of opiate withdrawal syndrome. *Neuropsychopharmacology*, 9 (1): 77-81.

Gallimberti, L., Ferri, M., Ferrara, S.D., Fadda, F., Gessa, G.L. (1992). Gamma-Hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. *Alcoholism, Clinical and Experimental Research*, 16 (4): 673-676.

Gallimberti, L., Schifano, F., Forza, G., Miconi, L., Ferrara, S.D. (1994). Clinical efficacy of gamma-hydroxybutyric acid in treatment of opiate withdrawal. *European Archives of Psychiatry and Clinical Neuroscience*, 244 (3): 113-114.

Galloway, G. P., Frederick, S. L., Staggers, F. E. Jr., Gonzales, M., Stalcup, S. A., Smith, D. E. (1997). Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction*, 92 (1): 89-96.

Gau, S.S., Chong, M.Y., Yang, P., Yen, C.F., Liang, K.Y., Cheng, A.T. (2007). Psychiatric and psychosocial predictors of substance use disorders among adolescents: longitudinal study. *The British Journal of Psychiatry*, 190: 42-48.

Ginsberg, J., Mohebbi, M.H., Patel, R.S., Brammer, L., Smolinski, M.S., Brilliant, L. (2009). Detecting influenza epidemics using search engine query data. *Nature*, 457 (7232): 1012-1014.

Ginsburg, B.C., McMahon, L.R., Sanchez, J.J., Javors, M.A. (2012). Purity of synthetic cannabinoids sold online for recreational use. *Journal of Analytical Toxicology*, 36(1): 66-68.

Goldsmith, R. J. (1993). An integrated psychology for the addictions: Beyond the self-medication hypothesis. *Journal of Addictive Disorders, 12*(3): 139–154.

Goldstein, P.J. (1985). The drugs/violence nexus: A tripartite conceptual framework. *Journal of Drug Issues*, 15 (4): 493–506.

Golsteijn, R., Peels, D., Evers, S., Bolman, C., Mudde, A., de Vries, H., Lechner, L. (2014). Cost-effectiveness and cost-utility of a Web-based or print-delivered tailored intervention to promote physical activity among adults aged over fifty: an economic evaluation of the Active Plus intervention. The *International Journal of Behavioral Nutrition and Physical Activity*, 11 (1): 122.

Gonzalez, A., Nutt, D.J. (2005). Gamma hydroxy butyrate abuse and dependency. *Journal of Psychopharmacology*, 19 (2): 195-204.

Gossop, M., Griffiths, P., Powis, B., Strang, J. (1992). Severity of dependence and route of administration of heroin, cocaine and amphetamines. *British Journal of Addiction*, 87 (11): 1527-1536.

Goullé, J.P., Chèze, M., Pépin, G. (2003). Determination of endogenous levels of GHB in human hair. Are there possibilities for the identification of GHB administration through hair analysis in cases of drug-facilitated sexual assault? *Journal of Analytical Toxicology*, 27(8): 574-580.

Gunderson, E.W., Haughey, H.M., Ait-Daoud, N., Joshi, A.S., Hart, C.L. (2014). A survey of synthetic cannabinoid consumption by current cannabis users. *Substance Abuse*, 35(2): 184-189.

Halkitis, P.N., Palamar, J.J., Mukherjee, P.P. (2007). Poly-club-drug Use among Gay & Bisexual Men: A Longitudinal Analysis. *Drug and Alcohol Dependence*, 89 (2-3): 153-160.

Hatsukami, D.K., Fischman, M.W. (1996). Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? *JAMA*, 276 (19): 1580-1588.

Heinz, A.J., Disney, E.R., Epstein, D.H., Glezen, L.A., Clark, P.I., Preston, K.L. (2010). A focus-group study on spirituality and substance-abuse treatment. *Substance Use & Misuse*, 45 (1-2): 134-153.

Helander, A., Bäckberg, M., Hultén, P., Al-Saffar, Y., Beck, O. (2014). Detection of new psychoactive substance use among emergency room patients: Results from the Swedish STRIDA project. *Forensic Science International*, 243C: 23-29.

Hermanns-Clausen, M., Kneisel, S., Szabo, B., Auwärter, V. (2013). Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction*, 108 (3): 534-544.

Hermle, L., Spitzer, M., Borchardt, D., Kovar, K. A., Gouzoulis, E. (1993). Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? *Neuropsychopharmacology*, 8 (2): 171-176.

Hillebrand J, Olszewski D, Sedefov R. (2008). *GHB and its precursor GBL: an emerging trend case study*. European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

Hyman, S.M., Sinha, R. (2009). Stress-related factors in cannabis use and misuse: implications for prevention and treatment. *Journal of Substance Abuse Treatment*, 36(4): 400-413.

Iqbal, M., Monaghan, T., Redmond, J. (2012). Manganese toxicity with ephedrone abuse manifesting as parkinsonism: a case report. *Journal of Medical Case Reports*, 6:52. doi: 10.1186/1752-1947-6-52.

James, D., Adams, R.D., Spears, R., Cooper, G., Lupton, D.J., Thompson, J.P., Thomas, S.H., National Poisons Information Service. (2011). Clinical characteristics of mephedrone toxicity reported to the U.K. National Poisons Information Service. *Emergency Medicine Journal*, 28(8): 686-689.

Jansen, K.L., Theron, L. (2006). Ecstasy (MDMA), methamphetamine, and date rape (drug-facilitated sexual assault): a consideration of the issues. *Journal of Psychoactive Drugs*, 38 (1): 1-12.

Johnson, M.W., Griffiths, R.R. (2013). Comparative abuse liability of GHB and ethanol in humans. *Experimental and Clinical Psychopharmacology*, 21(2): 112-123.

Kalix, P. (1992). Cathinone, a natural amphetamine. *Pharmacology & Toxicology*, 70 (2), 77-86.

Kam, P.C., Yoong, F.F. (1998). Gamma-hydroxybutyric acid: an emerging recreational drug. *Anaesthesia*, 53 (12): 1195-1198.

Kapitány-Fövény, M. (2014). *Az új pszichoaktív szerek használóinak demográfiai és pszichológiai sajátosságai*. Új szerek – Új (kliens) utak? A Magyar Addiktológiai Társaság konferenciája, Budapest. 2014.03.27.-2014.03.28., p.1.

Kapitány-Fövény, M., Farkas, J., Csorba, J., Szabó, T., Demetrovics, Zs. (2013b). *Különbségek a szintetikus kannabinoidok és a kannabisz szubjektív hatásaiban, a használati mintázatban és a használat okaiban*. Magyar Addiktológiai Társaság IX. Országos Kongresszus, Siófok, 2013.11.21-2013.11.23., p. 25.

Kapitány-Fövény, M., Kertész, M., Winstock, A., Deluca, P., Corazza, O., Farkas, J., Zacher, G., Urbán, R., Demetrovics, Zs. (2013a). Substitutional potential of mephedrone: an analysis of the subjective effects. *Human Psychopharmacology*, 28(4): 308-316.

Kapitány-Fövény, M., Mervó, B., Kertész, M., Corazza, O., Farkas, J., Kökönyei, Gy., Urbán, R., Demetrovics, Zs. (in press-a). Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone? *Human Psychopharmacology*, doi: 10.1002/hup.2490

Kapitány-Fövény, M., Mervó, B., Corazza, O., Kökönyei, Gy., Farkas, J., Urbán, R., Zacher, G., Demetrovics, Zs. (in press-b). Enhancing sexual desire and experience: An investigation on the sexual correlates of gamma-hydroxybutyrate (GHB) use. *Human Psychopharmacology*, doi: 10.1002/hup.2491

Karila, L., Novarin, J., Megarbane, B., Cottencin, O., Dally, S., Lowenstein, W., Reynaud, M.. (2009). Gamma-hydroxybutyric acid (GHB): more than a date rape drug, a potentially addictive drug. *Presse Médicale*, 38 (10): 1526-1538.

Kelly, B.C., Parsons, J.T., Wells, B.E. (2006). Prevalence and predictors of club drug use among club-going young adults in New York city. *Journal of Urban Health*, 83 (5): 884-895.

Kerr, T., Fairbairn, N., Tyndall, M., Marsh, D., Li, K., Montaner, J., Wood, E. (2007). Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and Alcohol Dependence*, 87(1): 39-45.

Khantzian, E. J. (1975). Self selection and progression in drug dependence. *Psychiatry Digest,* 36, 19–22.

Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *The American Journal of Psychiatry*, 142 (11): 1259-1264.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard Review of Psychiatry*, 4(5): 231–244.

Khantzian, E. J. (1999). *Treating Addiction as a Human Process: A Plea for a Measure of Marginality*. New York: Jason Aronson.

Khantzian, E. J., Halliday, K. S., McAuliffe, W. E. (1990). *Addiction and the Vulnerable Self: Modified Dynamic Group Therapy for Substance Abusers.* New York: Guilford.

Khoury, L., Tang, Y.L., Bradley, B., Cubells, J.F., Ressler, K. J. (2010). Substance use, childhood traumatic experience, and Posttraumatic Stress Disorder in an urban civilian population. *Depression and Anxiety*, 27(12): 1077–1086.

Kim, S.Y., Anderson, I.B., Dyer, J.E., Barker, J.C., Blanc, P.D. (2007). High-risk behaviors and hospitalizations among gamma hydroxybutyrate (GHB) users. *The American Journal of Drug and Alcohol Abuse*, 33(3):429-438.

Kirisci, L., Mezzich, A.C., Reynolds, M., Tarter, R.E., Aytaclar, S. (2009). Prospective study of the association between neurobehavior disinhibition and peer environment on illegal drug use in boys and girls. *The American Journal of Drug and Alcohol Abuse*, 35(3): 145-150.

Klein, M., Kramer, F. (2004). Rave drugs: pharmacological considerations. *AANA Journal*, 72 (1): 61-67.

Kolli, V., Sharma, A., Amani, M., Bestha, D., Chaturvedi, R. (2013). "Meow meow" (mephedrone) and catatonia. *Innovations in Clinical Neuroscience*, 10(2): 11-12.

Koob, G. F., Le Moal, M. (1997). Drug abuse: Hedonic homeostatic dysregulation. *Science,* 278 (5335): 52–58.

Korninger, C., Roller, R.E., Lesch, O.M. (2003). Gamma-hydroxybutyric acid in the treatment of alcohol withdrawal syndrome in patients admitted to hospital. *Acta Medica Austriaca*, 30 (3): 83–86.

Krueger, D.W. (1981). Stressful life events and the return to heroin use. *Journal of Human Stress*, 7(2): 3-8.

Krul, J., Girbes, A.R. (2011). γ-Hydroxybutyrate: experience of 9 years of γ-hydroxybutyrate (GHB)-related incidents during rave parties in The Netherlands. *Clinical Toxicology (Philadelphia, Pa)*, 49 (4): 311-315.

Kurtz, S.P., Inciardi, J.A., Pujals, E. (2009). Criminal activity among young adults in the Club Scene. *Law Enforcement Executive Forum*, 9(2): 47-59.

Kyle, P.B., Iverson, R.B., Gahagowni, R.G., Spencer, L. (2011). Illicit bath salts: not for bathing. *Journal of the Mississippi State Medical Association*, 52 (12): 375-377.

Laborit, H. (1972). Correlations between protein and serotonin synthesis during various activities of the central nervous system (slow and desynchronised) sleep, learning and memory,

sexual activity, morphine tolerance, aggressiveness and pharmacological action of sodium gamma-hydroxybutyrate. *Research Communications in Chemical Pathology and Pharmacology*, 3 (1): 51-81.

Laborit, H., Jouany, J.M., Gerard, J., Fabiani, F. (1960). Generalities concerning the experimental study and clinical use of gamma hydroxybutyrate of Na. *Agressologie,* 1: 397-406.

Lammers, G.J., Arends, J., Declerck, A.C., Ferrari, M.D., Schouwink, G., Troost, J. (1993). Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep*, 16 (3): 216-220.

Lankenau, S.E., Clatts, M.C. (2005). Patterns of polydrug use among ketamine injectors in New York City. *Substance Use & Misuse*, 40(9-10): 1381-1397.

Lea, T., Reynolds, R., De Wit, J. (2011). Mephedrone use among same-sex attracted young people in Sydney, Australia. *Drug and Alcohol Review*, 30 (4): 438-440.

Ledberg, A. (2015). The interest in eight new psychoactive substances before and after scheduling. *Drug and Alcohol Dependence*, 152: 73-78.

Lee, S.J., Levounis, P. (2008). Gamma hydroxybutyrate: an ethnographic study of recreational use and abuse. *Journal of Psychoactive Drugs*, 40 (3): 245-253.

Lembke, A. (2012). Time to abandon the self-medication hypothesis in patients with psychiatric disorders. *The American Journal of Drug and Alcohol Abuse*, 38(6): 524-529.

Liechti, M.E., Kunz, I., Greminger, P., Speich, R., Kupferschmidt, H. (2006). Clinical features of gamma-hydroxybutyrate and gamma-butyrolactone toxicity and concomitant drug and alcohol use. *Drug and Alcohol Dependence*, 81 (3):323-326.

Lindhout, I.E., Markus, M.T., Hoogendijk, T.H., Boer, F. (2009). Temperament and parental child-rearing style: unique contributions to clinical anxiety disorders in childhood. *European Child & Adolescent Psychiatry*, 18(7): 439-446.

Lisak, D. (1994). The psychological impact of sexual abuse: content analysis of interviews with male survivors. *Journal of Traumatic Stress*, 7 (4): 525-548.

Low, N.C., Dugas, E., O'Loughlin, E., Rodriguez, D., Contreras, G., Chaiton, M., O'Loughlin, J. (2012). Common stressful life events and difficulties are associated with mental health symptoms and substance use in young adolescents. *BMC Psychiatry*, 12: 116. doi: 10.1186/1471-244X-12-116.

Lu, J.J., Erickson, T.B. (2010). Gamma-Hydroxybutyrate. In: Holstege, C.P, Neer, T.M., Saathoff, G.B., Furbee, R.B. (Eds.). *Criminal Poisoning: Clinical And Forensic Perspectives*. Jones and Bartlett Publishers, Sudbury: Massachusetts, pp. 83-90.

Maddahian, E., Newcomb, M.D., Bentler, P.M. (1986). Adolescents' substance use: impact of ethnicity, income, and availability. *Advances in Alcohol & Substance Abuse*, 5(3): 63-78.

Maitre, M., Hechler, V., Vayer, P., Gobaille, S., Cash, C.D., Schmitt, M., Bourguignon, J.J. (1990). A specific gamma-hydroxybutyrate receptor ligand possesses both antagonistic and anticonvulsant properties. *The Journal of Pharmacology and Experimental Therapeutics*, 255 (2): 657-663.

Mamelak M. (1989). Gammahydroxybutyrate: an endogenous regulator of energy metabolism. *Neuroscience and Biobehavioral Reviews*, 13 (4): 187-198.

Mamelak, M., Scharf, M.B., Woods, M. (1986). Treatment of narcolepsy with GHB – a review of clinical and sleep laboratory findings. *Sleep*, 9 (1-2): 285-289.

Manchikanti, L., Cash, K.A., Damron, K.S., Manchukonda, R., Pampati, V., McManus, C.D. (2006). Controlled substance abuse and illicit drug use in chronic pain patients: An evaluation of multiple variables. *Pain Physician*, 9(3): 215-225.

Mansergh, G., Colfax, G.N., Marks, G., Rader, M., Guzman, R., Buchbinder, S. (2001). The circuit party men's health survey: Findings and implications for gay and bisexual men. *American Journal of Public Health*, 91 (6): 953–958.

Marsden, J., Gossop, M., Stewart, D., Rolfe, A., Farrell, M. (2000). Psychiatric symptoms among clients seeking treatment for drug dependence. Intake data from the National Treatment Outcome Research Study. *The British Journal of Psychiatry*, 176 (3): 285-289.

Marshall, B.D., Galea, S., Wood, E., Kerr, T. (2011). Injection methamphetamine use is associated with an increased risk of attempted suicide: a prospective cohort study. *Drug and Alcohol Dependence*, 119 (1-2): 134-137.

Martin, G., Bergen, H.A., Roeger, L., Allison, S. (2004). Depression in young adolescents: investigations using 2 and 3 factor versions of the Parental Bonding Instrument. *The Journal of Nervous and Mental Disease*, 192(10): 650-657.

Martinotti, G., Lupi, M., Acciavatti, T., Cinosi, E., Santacroce, R., Signorelli, M.S., Bandini, L., Lisi, G., Quattrone, D., Ciambrone, P., Aguglia, A., Pinna, F., Calò, S., Janiri, L., di Giannantonio, M. (2014). Novel psychoactive substances in young adults with and without psychiatric comorbidities. *BioMed Research International*, 2014:815424. doi: 10.1155/2014/815424.

Marusich, J.A., Antonazzo, K.R., Wiley, J.L., Blough, B.E., Partilla, J.S., Baumann, M.H. (2014). Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4-methylenedioxypyrovalerone (MDPV). *Neuropharmacology*, 87: 206-213.

Maskell, P.D., De Paoli, G., Seneviratne, C., Pounder, D.J. (2011). Mephedrone (4-methylmethcathinone)-related deaths. *Journal of Analytical Toxicology*, 35 (3): 188-191.

Matthews, A.J., Bruno, R. (2010). *Mephedrone use among regular ecstasy consumers in Australia. EDRS Drug Trends Bulletin, December*. Sydney: National Drug and Alcohol Research Centre, University of New South Wales.

Mattick, R.P., Topp, L., Degenhardt, L. (2004). A reduction in the availability of heroin in Australia. *Bulletin on Narcotics*, 56 (1-2), 65-88.

Mattison, A.M., Ross, M.W., Wolfson, T., Franklin, D., San Diego HIV Neurobehavioral Research Center Group. (2001). Circuit party attendance, club drug use and unsafe sex in gay men. *Journal of Substance Abuse*, 13 (1-2): 119-126.

McDonough, M., Kennedy, N., Glasper, A., Bearn, J. (2004). Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug and Alcohol Dependence*, 75(1): 3-9.

McDowell, D. (2000). Gay men, lesbians and substances of abuse and the "club and circuit party scene": What clinicians should know. *Journal of Gay & Lesbian Psychotherapy*, 3 (3-4): 37–57.

McElrath, K., O'Neill, C. (2011). Experiences with mephedrone pre- and post-legislative controls: perceptions of safety and sources of supply. *The International Journal on Drug Policy*, 22(2): 120-127.

McGue, M., Iacono, W. G. (2008). The adolescent origins of substance use disorders. *International Journal of Methods in Psychiatric Research*, 17(Suppl 1): 30-38.

McMillen, C., Howard, M.O., Nower, L., Chung, S. (2001). Positive by-products of the struggle with chemical dependency. *Journal of Substance Abuse Treatment*, 20(1): 69-79.

McPeake, J.D., Kennedy, B.P., Gordon, S.M. (1991). Altered states of consciousness therapy. A missing component in alcohol and drug rehabilitation treatment. *Journal of Substance Abuse Treatment*, 8(1-2):75-82.

Merle, R. (1997). 'Special-K' is latest U.S. drug fad. *The Seattle Times*, June 20.

Meunier, D., Ersche, K.D., Craig, K.J., Fornito, A., Merlo-Pich, E., Fineberg, N.A., Shabbir, S.S., Robbins, T.W., Bullmore, E.T. (2012). Brain functional connectivity in stimulant drug dependence and obsessive-compulsive disorder. *NeuroImage*, 59(2):1461-1468.

Michael, G.W., Hall, J.N. (1994). South Florida at risk for Grievous Bodily Harm. Information for Action. *Drug Surveillance News*, May 9.

Midanik, L.T., Tam, T.W., Weisner, C. (2007). Concurrent and simultaneous drug and alcohol use: results of the 2000 National Alcohol Survey. *Drug and Alcohol Dependence*, 90(1): 72-80.

Milinovich, G.J., Magalhães, R.J., Hu, W. (2015). Role of big data in the early detection of Ebola and other emerging infectious diseases. *Lancet Glob Health*, 3(1): e20-21.

Miotto, K., Darakjian, J., Basch, J., Murray, S., Zogg, J., Rawson, R. (2001). Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *The American Journal on Addictions*, 10 (3): 232-241.

Mordal, J., Holm, B., Gossop, M., Romøren, M., Mørland, J., Bramness, J. (2011). Psychoactive substance use among patients admitted to an acute psychiatric ward: laboratory findings and associations with clinical characteristics. *Nordic Journal of Psychiatry*, 65 (3): 208-215.

Móró, L., Rácz, J. (2013). Online drug user-led harm reduction in Hungary: a review of "Daath". *Harm Reduction Journal*, 10:18.

Murray, B.L., Murphy, C.M., Beuhler, M.C. (2012). Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypyrovalerone (MDPV). *Journal of Medical Toxicology*, 8(1): 69-75.

Mutasa, H.C. (2001). Risk factors associated with noncompliance with methadone substitution therapy (MST) and relapse among chronic opiate users in an Outer London community. *Journal of Advanced Nursing*, 35(1): 97-107.

Muthén, L.K., Muthén, B.O. (1998-2007). *Mplus User's Guide. Fifth Edition*. Los Angeles, CA: Muthén & Muthén

Nabben, T., Benschop, A., Korf, D. (2006). *Antenne 2005: trends in alcohol, tabak en drugs bij jonge Amsterdammers*. Rozenberg Publishers, Amsterdam.

Nacca, N., Vatti, D., Sullivan, R., Sud, P., Su, M., Marraffa, J. (2013). The synthetic cannabinoid withdrawal syndrome. *Journal of Addiction Medicine*, 7(4): 296-298.

NACD and PHIRB (National Advisory Committee on Drugs and Public Health Information and Research Branch) (2011). *Drug use in Ireland and Northern Ireland: first results from the 2010/2011 drug prevalence survey* [Online]. Available:http://www.drugs.ie/resourcesfiles/research/2011/NACDdrug_use_irelandNov2011.pdf

Najavits, L.M., Weiss, R.D., Shaw, S.R. (1997). The link between substance abuse and posttraumatic stress disorder in women. A research review. *The American Journal on Addictions*, 6(4), 273-283.

Nation, M., Heflinger, C.A. (2006). Risk factors for serious alcohol and drug use: the role of psychosocial variables in predicting the frequency of substance use among adolescents. *The American Journal of Drug and Alcohol Abuse*, 32(3): 415-433.

Nava, F., Premi, S., Manzato, E., Campagnola, W., Lucchini, A., Gessa, G.L. (2007). Gamma-hydroxybutyrate reduces both withdrawal syndrome and hypercortisolism in severe abstinent alcoholics: an open study vs. diazepam. *The American Journal of Drug and Alcohol Abuse*, 33 (3): 379–392.

Németh, Zs., Kun, B., Demetrovics, Zs. (2010). The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. *Journal of Psychopharmacology*, 24 (9):1281-1287.

Nemzeti Drog Fókuszpont (2012). *"MAGYARORSZÁG" Új fejlemények, trendek és részletes információk a kiemelt témákról. 2012-es ÉVES JELENTÉS az EMCDDA számára*. [Online] Available: http://drogfokuszpont.hu/wp-content/uploads/EMCDDA_jelentes_2012.pdf

Newcombe, R. (2009). *The Use of Mephedrone (M-cat,Meow) in Middlesbrough*. Lifeline Publications and Research, Manchester, UK.

Nicholson, K.L., Balster, RL. (2001). GHB: a new and novel drug of abuse. *Drug and Alcohol Dependence*, 63 (1): 1-22.

Nimmerrichter, A.A., Walter, H., Gutierrez-Lobos, K.E., Lesch, O.M. (2002). Double blind controlled trial of γ-hydroxybutyrate and clomethiazole in the treatment of alcohol withdrawal. *Alcohol and Alcoholism*, 37 (1): 67–73.

Nissbrandt, H.G., Engberg, G. (1996). The $GABA_B$-receptor antagonist, CGP 35348, antagonises γ-hydroxybutyrate- and baclofen-induced alterations in locomotor activity and forebrain dopamine levels in mice. *Journal of Neural Transmissions*, 103 (11): 1255-1263.

Novak, S.P., Kral, A.H. (2011). Comparing injection and non-injection routes of administration for heroin, methamphetamine, and cocaine users in the United States. *Journal of Addictive Diseases*, 30 (3): 248-257.

Oliveto, A., Gentry, W.B., Pruzinsky, R., Gonsai, K., Kosten, T.R., Martell, B., Poling, J. (2010). Behavioral effects of gamma-hydroxybutyrate in humans. *Behavioural Pharmacology*, 21(4): 332-342.

Paksi, B., Rózsa, S., Kun, B., Arnold, P., Demetrovics, Zs. (2009). A magyar népesség addiktológiai problémái: az Országos Lakossági Adatfelvétel az Addiktológiai Problémákról (OLAAP) reprezentatív felmérés módszertana és a minta leíró jellemzői. *Mentálhigiéné és Pszichoszomatika*, 10 (4): 273-300.

Palamar, J.J., Halkitis, P.N. (2006). A qualitative analysis of GHB use among gay men: Reasons for use despite potential adverse outcomes. *The International Journal on Drug Policy*, 17 (1): 23–28.

Palamar, J.J., Mukherjee, P.P., Halkitis, P.N. (2008). A longitudinal investigation of powder cocaine use among club-drug using gay and bisexual men. *Journal of Studies on Alcohol and Drugs*, 69(6):806-813.

Parrott, A. C., Lasky, J. (1998). Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology*, 139 (3): 261-268.

Parrott, A. C., Lees, A., Garnham, N. J., Jones, M., Wesnes, K. (1998). Cognitive performance in recreational users of MDMA of 'ecstasy': evidence for memory deficits. *Journal of Psychopharmacology*, 12 (1): 79-83.

Parrott, A.C., Milani, R.M., Parmar, R., Turner, J.D. (2001). Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology (Berl)* 159 (1): 77-82.

Parsons, J.T., Grov, C., Kelly, B.C. (2009). Club drug use and dependence among young adults recruited through time-space sampling. *Public Health Reports*, 124 (2): 246-254.

Paykel, E. S. (1991). Stress and life events. In: Davidson, L., Linnoila, M. (eds). *Risk factors for youth suicide*. New York: Hemisphere

Peroutka, S. J., Newman, H., Harris, H. (1988). Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology*, 1 (4): 273–277.

Persson, H.E., Sjöberg, G.K., Haines, J.A., Pronczuk de Garbino, J. (1998). Poisoning Severity Score. Grading of acute poisoning. *Journal of Toxicology, Clinical Toxicology*, 36 (3): 205-213.

Péterfi, A., Tarján, A., Horváth, G.C., Csesztregi, T., Nyírády, A. (2014). Changes in patterns of injecting drug use in Hungary: a shift to synthetic cathinones. *Drug Testing and Analysis*, 6(7-8): 825-831.

Peters, A., Davies, T., Richardson, A. (1998). Multi-site samples of injecting drug users in Edinburgh: prevalence and correlates of risky injecting practices. *Addiction*, 93(2): 253-267.

Power, M. (2009). Mephedrone: The future of drug dealing? *Druglink*, 25 (1): 7-13.

Preston, K.L., Silverman, K., Schuster, C. R., Cone, E. J. (1997). Comparison of self-reported drug use with quantitative and qualitative urinanalysis for assessment of drug use in treatment studies. In Harrison, L., Hughes, A. (Eds.). *The validity of self-reported drug use: Improving the accuracy of survey estimates. National Institutes of Health (NIDA) Research Monograph 167*. NIH Publication No. 97-4147, pp. 130-145.

Prosser, J.M., Nelson, L.S. (2012). The toxicology of bath salts: a review of synthetic cathinones. *Journal of Medical Toxicology*, 8(1): 33-42.

Psychonaut Web Mapping Research Group (2009). *Mephedrone report*. Institute of Psychiatry, King's College London: London UK available at: http://www.psychonautproject.eu/documents/reports/Mephedrone.pdf

Quest, D.W., Horsley, J. (2007). Field-test of a date-rape drug detection device. *Journal of Analytical Toxicology*, 31(6): 354-357.

Rácz, J. (2000). *Prevenciós programok értékelése*. Ifúsági és Sportminisztérium, Budapest.

Rácz, J. (2006). *Kvalitatív drogkutatások*. L'Harmattan Kiadó, Budapest

Rácz, J., Csák, R., Faragó, R., Vadász, V. (2012). The phenomenon of drug change in the interviews with injecting drug users. *Psychiatria Hungarica*, 27 (1): 29-47.

Ramo, D.E., Grov, C., Delucchi, K., Kelly, B.C., Parsons, J.T. (2010). Typology of club drug use among young adults recruited using time-space sampling. *Drug and Alcohol Dependence*, 107(2-3): 119-127.

Reed, P. L., Anthony, J. C., Breslau, N. (2007). Incidence of drug problems in young adults exposed to trauma and posttraumatic stress disorder. *Archives of General Psychiatry*, 64 (12): 1235–1442.

Ren, J., Ning, Z., Asche, C.V., Zhuang, M., Kirkness, C.S., Ye, X., Fu, J., Pan, Q. (2013). Trends and predictors in methadone maintenance treatment dropout in Shanghai, China: 2005-2011. *Current Medical Research and Opinion*, 29(7): 731-738.

Robertson, J.A., Plant, M.A. (1988). Alcohol, sex and risks of HIV infection. *Drug and Alcohol Dependence*, 22 (1-2): 75-78.

Romanelli, F., Smith, K.M., Pomeroy, C. (2003). Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Topics in HIV Medicine*, 11 (1): 25-32.

Rosario, M., Reisner, S.L., Corliss, H.L., Wypij, D., Calzo, J., Austin, S.B. (2014). Sexual-orientation disparities in substance use in emerging adults: a function of stress and attachment paradigms. *Psychology of Addictive Behaviors*, 28(3): 790-804.

Rosen, M.I., Pearsall, H.R., Woods, S.W., Kosten, T.R. (1997). Effects of gamma-hydroxybutyric acid (GHB) in opioid-dependent patients. *Journal of Substance Abuse Treatment*, 14 (2): 149-154.

Rosenberg, M.H., Deerfield, L.J., Baruch, E.M. (2003). Two cases of severe gamma-hydroxybutyrate withdrawal delirium on a psychiatric unit: recommendations for management. *The American Journal of Drug and Alcohol Abuse*, 29(2): 487-496.

Ross, E.A., Reisfield, G.M., Watson, M.C., Chronister, C.W., Goldberger, B.A. (2012). Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone. *The American Journal of Medicine*, 125(9):854-858.

Roth, R.H. (1970). Formation and regional distribution of gamma-hydroxybutyric acid in mammalian brain. *Biochemical Pharmacology*, 19 (12): 3013-3019.

Roussel, O., Perrin, M., Herard, P., Chevance, M., Arpino, P. (2009). La 4- méthyléphédrone sera-t-elle une "Ecstasy" du XXIème siècle? *Annales de Toxicologie Analytique*, 21 (4): 169–177.

Sable, M.R., Danis, F., Mauzy, D.L., Gallagher, S.K. (2006). Barriers to reporting sexual assault for women and men: perspectives of college students. *Journal of American College Health*, 55 (3): 157-162.

Saha, K., Partilla, J.S., Lehner, K.R., Seddik, A., Stockner, T., Holy, M., Sandtner, W., Ecker, G.F., Sitte, H.H., Baumann, M.H. (2015). 'Second-Generation' Mephedrone Analogs, 4-MEC and 4-MePPP, Differentially Affect Monoamine Transporter Function. *Neuropsychopharmacology*, 40 (6): 1321-1331.

Sauer, C., Arens, E.A., Stopsack, M., Spitzer, C., Barnow, S. (2014). Emotional hyper-reactivity in borderline personality disorder is related to trauma and interpersonal themes. *Psychiatry Research*, 220(1-2): 468-476.

Scharf, M.B., Brown, D., Woods, M., Brown, L., Hirschowitz, J. (1985). The effects and effectiveness of GHB in patients with narcolepsy. *The Journal of Clinical Psychiatry*, 46 (6): 222-225.

Schifano, F., Albanese, A., Fergus, S., Stair, J. L., Deluca, P., Corazza, O., Davey, Z., Corkery, J., Siemann, H., Scherbaum, N., Farre, M., Torrens, M., Demetrovics, Zs., Ghodse, A. H., Psychonaut Web Mapping, ReDNet Research Groups (2010). Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology* (*Berl*), 214 (3): 593-602.

Schifano, F., Corkery, J., Ghodse, A.H. (2012). Suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone, "meow meow") in the United Kingdom. *Journal of Clinical Psychopharmacology*, 32(5): 710-714.

Schifano, F., Deluca, P., Agosti, L., Martinotti, G., Corkery, J.M., Alex, B., Caterina, B., Heikki, B., Raffaella, B., Anna, C., Lucia, D.F., Dorte, D.R., Magi, F., Susana, F., Irene, F., Claude, G., Lisbet, H., Lene, S.J., Mauro, L., Christopher, L., Aino, M., Teuvo, P., Milena, P., Salman, R., Damien, R., Angela, R.M., Francesco, R., Norbert, S., Holger, S., Josep, T., Marta, T., Francesco, Z.; Psychonaut 2002 Research Group. (2005). New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ('Blue Mystic'). *Journal of Psychopharmacology*, 19(6): 675-679.

Schiff, M., Levit, S., Cohen-Moreno, R. (2010). Childhood sexual abuse, post-traumatic stress disorder, and use of heroin among female clients in Israeli methadone maintenance treatment programs (MMTPS). *Social Work in Health Care*, 49(9): 799-813.

Schneider, S., Meys, F. (2011). Analysis of illicit cocaine and heroin samples seized in Luxembourg from 2005-2010. *Forensic Science International*, 212 (1-3): 242-246.

Scott-Ham, M., Burton, F.C. (2005). Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. *Journal of Clinical Forensic Medicine*, 12 (4): 175-186.

Scrima, L., Hartman, P.G., Johnson, F.H. Jr, Thomas, E.E., Hiller, F.C. (1990). The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. *Sleep* 13 (6): 479-490.

Semple, S.J., Patterson, T.L., Grant, I. (2004). A comparison of injection and non-injection methamphetamine-using HIV positive men who have sex with men. *Drug and Alcohol Dependence*, 76 (2): 203-212.

Shacham, E., Cottler, L.B. (2010). Sexual behaviors among club drug users: prevalence and reliability. *Archives of Sexual Behavior*, 39 (6): 1331-1341.

Shulgin, A. T., Nichols, D. E. (1978). Characterization of three new psychotomimetics. In Stillman, R. C., Willette, R. E. (Eds.) *The Pharmacology of Hallucinogens*. New York: Pergamon.

Simmler, L.D., Buser, T.A., Donzelli, M., Schramm, Y., Dieu, L.H., Huwyler, J., Chaboz, S., Hoener, M.C., Liechti, M.E. (2013). Pharmacological characterization of designer cathinones in vitro. *British Journal of Pharmacology*, 168(2): 458-470.

Simmler, L.D., Rickli, A., Hoener, M.C., Liechti, M.E. (2014). Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. *Neuropharmacology*, 79: 152-160.

Simmons, M.M., Cupp, M.J. (1998). Use and abuse of flunitrazepam. *The Annals of Pharmacotherapy*, 32 (1): 117–119.

Sindicich, N., Cassar, J., Burns, L. (2011). National Trends in Ecstasy and Related Drug Markets around Australia. *The Open Addiction Journal*, 4: 54.

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences*, 1141: 105-130.

Smit, E.S., Ever, S., de Vries, H., Hoving, C. (2013). Cost-Effectiveness and Cost-Utility of Internet-Based Computer Tailoring for Smoking Cessation. *Journal of Medical Internet Research*, 15(3): e57.

Smith, K., Flatley, J. (2011). *Drug Misuse Declared: Findings from the 2010/11 British Crime Survey England and Wales*. Statistical Bulletin, UK Home Office.

Smith, S. W., Garlich, F.M. (2013). Availability and Supply of Novel Psychoactive Substances. In Dargan, P.I., Wood, D.M. (eds). *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*. Academic Press, Elsevier, UK. ISBN: 978-0-12-415816-0

Solowij, N., Hall, W., Lee, N. (1992). Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug. *British Journal of Addiction*, 87 (8): 1161-1172.

Sporer, K.A., Chin, R.L., Dyer, J.E., Lamb, R. (2003). Gamma-hydroxybutyrate serum levels and clinical syndrome after severe overdose. *Annals of Emergeny Medicine*, 42 (1): 3-8.

Stein, L.A., Lebeau, R., Clair, M., Martin, R., Bryant, M., Storti, S., Monti, P. (2011). A web-based study of gamma-hydroxybutyrate (GHB): patterns, experiences, and functions of use. *The American Journal on Addictions*, 20 (1): 30-39.

Steppan, M., Kraus, L., Piontek, D., Siciliano, V. (2013). Are cannabis prevalence estimates comparable across countries and regions? A cross-cultural validation using search engine query data. *The International Journal on Drug Policy*, 24 (1): 23–29.

Stewart, S.H., Ouimette, P., Brown, P.J. (2002). Gender and the comorbidity of PTSD with substance use disorders. In: Kimerling, R., Ouimette, P. (eds). *Gender and PTSD*. New York, NY: Guilford Press, pp. 232–270.

Strang, J., Bearn, J., Farrell, M., Finch, E., Gossop, M., Griffiths, P., Marsden, J., Wolff, K. (1998). Route of drug use and its implications for drug effect, risk of dependence and health consequences. *Drug and Alcohol Review*, 17 (2): 197-211.

Sumnall, H.R., Woolfall, K., Edwards, S., Cole, J.C., Beynon, C.M. (2008). Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). *Drug and Alcohol Dependence*, 92 (1-3): 286-290.

Teasdale, G., Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, 2 (7872): 81-84.

Tedeschi, R.G., Calhoun, L.G. (1996). The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. *Journal of Traumatic Stress*, 9(3): 455-471.

Thai, D., Dyer, J.E., Benowitz, N.L., Haller, C.A. (2006). Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *Journal of Clinical Psychopharmacology*, 26 (5): 524-529.

The National Treatment Agency for Substance Misuse (2012) *Club Drugs: Emerging Trends and Risks.* [Online] Available: http://www.nta.nhs.uk/uploads/clubdrugsreport2012%5B0%5D.pdf

Triffleman, E. (2003). Issues in implementing posttraumatic stress disorder treatment outcome research in community-based treatment programs. In: Sorensen, J.L., Rawson, R.A., Guydish, J., Zweben, J.E. (eds). *Drug abuse treatment through collaboration: Practice and research partnerships that work*.Washington, DC: American Psychological Association, pp. 227–247.

Tu, Y-K., Gunnell, D., Gilthorpe, M.S. (2008). Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon—the reversal paradox. *Emerging Themes in Epidemiology*, 5:2. doi:10.1186/1742-7622-5-2

Tunnicliff, G. (1992). Significance of gamma-hydroxybutyric acid in the brain. *General Pharmacology*, 23 (6): 1027-1034.

Turner, C.F., Ku, L., Rogers, S.M., Lindbergh, L.D., Pleck, J.H., Sonenstein, F.L. (1998). Adolescent sexual behavior, drug use, and violence. *Science*, 280 (5365): 867-873.

Tyndall, M.W., Currie, S., Spittal, P., Li, K., Wood, E., O'Shaughnessy, M.V., Schechter, M.T. (2003). Intensive injection cocaine use as the primary risk factor in the Vancouver HIV-1 epidemic. *AIDS*, 17 (6): 887-893.

UK Home Office (2012). *Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales (2nd Edition)*. [Online] Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147938/drugs-misuse-dec-1112-pdf.pdf

UNODC (2011). *World drug report 2011*. United Nations Office on Drugs and Crime, Vienna.

Urbán, R., Kun, B., Farkas, J., Paksi, B., Kökönyei, G., Unoka, Z., Felvinczi, K., Oláh, A., Demetrovics, Z. (2014). Bifactor structural model of symptom checklists: SCL-90-R and Brief Symptom Inventory (BSI) in a non-clinical community sample. *Psychiatry Research*, 216 (1): 146-154.

van Amsterdam, J.G., Brunt, T.M., McMaster, M.T., Niesink, R., van Noorden, M.S., van den Brink, W. (2012). Cognitive impairment due to intensive use and overdoses of gammahydroxybutyric acid (GHB). *Tijdschrift voor Psychiatrie*, 54 (12):1001-1010.

van Amsterdam, J.G., Brunt, T.M., Pennings, E., van den Brink, W. (2014). Risk assessment of GBL as a substitute for the illicit drug GHB in the Netherlands. A comparison of the risks of GBL versus GHB. *Regular Toxicology and Pharmacology*, 70 (2): 507-513.

Van Cauter, E., Plat, L., Scharf, M.B., Leproult, R., Cespedes, S., l'Hermite-Balériaux, M., Copinschi, G. (1997). Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young Men. *The Journal of Clinical Investigation*, 100 (3): 745–753.

Van Hout, M.C. (2014). Kitchen chemistry: A scoping review of the diversionary use of pharmaceuticals for non-medicinal use and home production of drug solutions. *Drug Testing an Analysis*, 6(7-8): 778-787.

Van Hout, M.C., Bingham, T. (2012). "A costly turn on": patterns of use and perceived consequences of mephedrone based head shop products amongst Irish injectors. *The International Journal on Drug Policy*, 23(3): 188-197.

van Laar, M.W., Cruts, G., van Gageldonk, A., Ooyen-Houben M, Croes, E., Meijer, R., Ketelaars, T. (2012). *The Netherlands Drug Situation – Report to the EMCDDA by the Reitox National Focal Point*. [Online] Available: http://www.trimbos.org/~/media/English%20site/AF1130%20The%20Netherlands%20Drug%20Situation%202011_web.ashx

Vandrey, R., Dunn, K.E., Fry, J.A., Girling, E.R. (2012). A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug and Alcohol Dependence*, 120(1-3): 238-241.

Varela, M., Nogué, S., Orós, M., Miró, Ò. (2004). Gamma hydroxybutyrate use for sexual assault. *Emergency Medicine Journal*, 21 (2): 255–256.

Vento, A.E., Martinotti, G., Cinosi, E., Lupi, M., Acciavatti, T., Carrus, D., Santacroce, R., Chillemi, E., Bonifaci, L., di Giannantonio, M., Corazza, O., Schifano, F. (2014). Substance use in the club scene of Rome: a pilot study. *BioMed Research International*, 2014:617546. doi: 10.1155/2014/617546.

Vermunt, J.K., Magidson, J. (2002). Latent class cluster analysis. In Hagenaars, J. A., McCutcheon, A. L. (eds.). *Advances in Latent Class Analysis*. Cambridge University Press.

Volkow, N.D., Wang, G.J., Fischman, M.W., Foltin, R., Fowler, J.S., Franceschi, D., Franceschi, M., Logan, J., Gatley, S.J., Wong, C., Ding, Y.S., Hitzemann, R., Pappas, N. (2000). Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sciences*, 67 (12): 1507-1515.

Vollenweider, F. X., Gamma, A., Liechti, M., Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacology*, 19 (4): 241-251.

Waidner, G. (1999). *Die Viktimisierungserfahrungen drogenabhängiger Personen. Eine Untersuchung mit qualitativen Verfahren*. Unveröffentlichte Diplomarbeit an der Grund- und Integrativwissenschaftlichen Fakultät der Universität Wien: Vienna.

Wardenaar, K.J., van Veen, T., Giltay, E.J., Zitman, F.G., Penninx, B.W. (2014). The use of symptom dimensions to investigate the longitudinal effects of life events on depressive and anxiety symptomatology. *Journal of Affective Disorders*, 156: 126-133.

Watterson, L.R., Hood, L., Sewalia, K., Tomek, S.E., Yahn, S., Johnson, C.T., Wegner, S., Blough, B.E., Marusich, J.A., Olive, M.F. (2012). The Reinforcing and Rewarding Effects of Methylone, a Synthetic Cathinone Commonly Found in "Bath Salts". *Journal of Addiction Research & Therapy*, Suppl 9. doi: 10.4172/2155-6105.S9-002.

Webster-Stratton, C., Hammond, M. (1999). Marital conflict management skills, parenting style, and early-onset conduct problems: processes and pathways. *Journal of Child Psychology and Psychiatry*, 40(6): 917-927.

Weidel, J.J., Provencio-Vasquez, E., Grossman, J. (2008). Sex and drugs: high-risk behaviors at circuit parties. *American Journal of Men's Health*, 2 (4): 344-352.

White, B., Day, C., Degenhardt, L., Kinner, S., Fry, C., Bruno, R., Johnston, J. (2006). Prevalence of injecting drug use and associated risk behavior among regular ecstasy users in Australia. *Drug and Alcohol Dependence*, 83 (3): 210-217.

Wilens, T.E., Adamson, J., Sgambati, S., Whitley, J., Santry, A., Monuteaux, M.C., Biederman, J. (2007). Do individuals with ADHD self-medicate with cigarettes and substances of abuse? Results from a controlled family study of ADHD. *The American Journal on Addictions*, 16 (Suppl 1): 14-21.

Winstock, A. R., Marsden, J. (2010). *Mephedrone: assessment of health risks and harms. European Monitoring Centre for Drugs and Drug Addiction. Risk assessment report of a new psychoactive substance: 4-methylmethcathinone (mephedrone).* Lisbon: EMCDDA.

Winstock, A. R., Marsden, J., Mitcheson, L. (2010). What should be done about mephedrone? *BMJ*, 340: c1605.

Winstock, A. R., Mitcheson, L., Deluca, P., Davey, Z., Corazza, O., Schifano, F. (2011a). Mephedrone, new kid for the chop? *Addiction*, 106 (1): 154-161.

Winstock, A.R. (2011). 'The 2011 Mixmag drugs survey'. *Mixmag March*: 49-59.

Winstock, A.R. (2012). *Early results of the headline findings from GDS 2012* [Online] Available: http://globaldrugsurvey.com/.

Winstock, A.R., Barratt, M.J. (2013). Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug and Alcohol Dependence*, 131 (1-2): 106-111.

Winstock, A.R., Mitcheson, L. (2010). *The annual Mixmag drugs survey 2010* [Online] Available: www.menincarter.net/mixmag/. [Accessed].

Winstock, A.R., Mitcheson, L., Ramsey, J., Davies, S., Puchnarewicz, M., Marsden, J. (2011b). Mephedrone: use, subjective effects and health risks. *Addiction*, 106 (11): 1991–1996.

Wisselink, D.J., Kuijpers, W.G.T., Mol, A., (2013). *Landelijk Alcohol en Drugs Informatiesysteem (LADIS). Kerncijfers Verslavingszorg 2012*. Online Available: http://www.sivz.nl/File/Kerncijfers%20Verslavingszorg%202012.pdf

Wood, D.M., Greene, S.L., Dargan, P.I. (2011). Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emergency Medicine Journal*, 28(4): 280-282.

Wood, D.M., Greene, S.L., Dargan, P.I. (2013). Five-year trends in self-reported recreational drugs associated with presentation to a UK emergency department with suspected drug-related toxicity. *European Journal of Emergency Medicine*, 20(4): 263-267.

Woods, J.H., Winger, G. (1997). Abuse liability of flunitrazepam. *Journal of Clinical Psychopharmacology*, 17(3-Supplement 2): 1–57.

Wyman, J.F., Lavins, E.S., Engelhart, D., Armstrong, E.J., Snell, K.D., Boggs, P.D., Taylor, S.M., Norris, R.N., Miller, F.P. (2013). Postmortem tissue distribution of MDPV following lethal intoxication by "bath salts". *Journal of Analytical Toxicology*, 37(3): 182-185.

Xie, X., Smart, T.G. (1992). Gamma-hydroxybutyrate hyperpolarizes hippocampal neurones by activating $GABA_B$ receptors. *European Journal of Pharmacology*, 212 (2-3): 291-294.

Xu, Y., Olfson, M., Villegas, L., Okuda, M., Wang, S., Liu, S.M., Blanco, C. (2013). A characterization of adult victims of sexual violence: results from the national epidemiological survey for alcohol and related conditions. *Psychiatry*, 76 (3): 223-240.

Yang, F., Lin, P., Li, Y., He, Q., Long, Q., Fu, X., Luo, Y. (2013). Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. *Harm Reduction Journal*, 10: 3. doi: 10.1186/1477-7517-10-3.

Yin, S., Ho, M. (2012). Monitoring a toxicological outbreak using Internet search query data. *Clinical Toxicology (Philadelphia, Pa)*, 50 (9): 818-822.

Zhai, D., Tan, Y.Q., Xu, W., Chang, Y.T. (2014). Development of a fluorescent sensor for illicit date rape drug GHB. *Chemical Communications (Cambridge, England)*, 50(22): 2904-2906.

Zheluk, A., Quinn, C., Meylakhs, P. (2014). Internet search and krokodil in the Russian Federation: an infoveillance study. *Journal of Medical Internet Research*, 16 (9): e212.

Zhou, X.C., Shen, H.B. (2010). Notifiable infectious disease surveillance with data collected by search engine. *Journal of Zhejiang University SCIENCE C*, 11 (4): 241-248.

Zinberg, N. (1986). *Drug, Set, and Setting: The Basis for Controlled Intoxicant Use*. New Haven, CT: Yale University Press.

Zvosec, D.L., Smith, S.W., Porrata, T., Strobl, A.Q., Dyer, J.E. (2011). Case series of 226 γ-hydroxybutyrate-associated deaths: lethal toxicity and trauma. *The American Journal of Emergency Medicine*, 29 (3): 319-332.

Zweben, J.E., Cohen, J.B., Christian, D., Galloway, G.P., Salinardi, M., Parent, D., Iguchi, M.; Methamphetamine Treatment Project (2004). Psychiatric symptoms in methamphetamine users. *The American Journal on Addictions*, 13 (2): 181-190.